IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK & CO., INC., Plaintiff, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	C.A. No. 06-310-GMS

DEFENDANT TEVA PHARMACEUTICALS USA, INC.'S OPENING BRIEF IN SUPPORT OF ITS MOTION UNDER FED. R. CIV. P. 11(b) FOR SANCTIONS AGAINST COUNSEL FOR PLAINTIFF MERCK & CO., INC.

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YOUNG CONAWAY STARGATT & TAYLOR, LLP
Josy W. Ingersoll (#1088)
Karen L. Pascale (#2903)
Adam W. Poff (#3990)
The Brandywine Building
100 West Street, 17th Floor
P.O. Box 391
Wilmington, DE 19899-0391
(302) 571-6600

Attorneys for Defendant,
Teva Pharmaceuticals USA, Inc.

OF COUNSEL:

James Galbraith
Maria Luisa Palmese
William G. James II
Huiya Wu
Colman B. Ragan
KENYON & KENYON LLP
One Broadway
New York, NY 10004-1007
(212) 425-7200

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INTRODUCTION

Teva Pharmaceuticals USA, Inc. ("Teva USA") brings this motion under Fed. R. Civ. P. 11(b) for sanctions against counsel for plaintiff Merck & Co., Inc. ("Merck"), for filing a baseless complaint in this action against Teva USA for an improper purpose. Merck's complaint seeks to reopen the judgment of the Federal Circuit Court of Appeals in *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1395 (Fed. Cir. 2005) (Complaint (D.I. 1), Ex. I), a patent infringement case that Merck lost. Merck and its lawyers know that the stated basis for the complaint – that Teva USA's counsel committed a fraud on the court in that case – is false, and Merck has brought the complaint solely to delay a related case, *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, Civil Action No. 04-939 (GMS), which is pending in this Court.

Essentially, Merck alleges that in the case Merck lost, Teva USA's counsel "concealed" and did not produce in discovery a United States patent application that had been filed by Teva USA's parent company, Teva Pharmaceuticals Ltd. ("Teva Ltd."). This application, referred to as "the '685 application" (D.I. 1, Ex. J), describes a preclinical study that employed beagles as the test animal. According to Merck, the "revelation" that Teva Ltd. used beagles in one preclinical study is inconsistent with Teva USA's criticism of another entirely different type of study that was described in Merck's patent in suit in that case, and that happened to employ beagles. According to Merck, the case was "close," and the alleged withholding of the '685 application "affected the outcome." (D.I. 1 at ¶ 47.)

Merck's complaint is fatuous. Merck's lawyers who appear on the complaint are the same lawyers who appeared in the prior case. Those lawyers know that the premise

and central allegations of the complaint are false: the '685 application is not a basis for any "revelation" of an allegedly "inconsistent" position. The attorneys who filed this complaint know that it was not "concealed" and that it is not "inconsistent" with Teva USA's position in that case.

Moreover, they also know that the trial and appeal record included another Teva Ltd. patent that described the same type of preclinical study and used the same methodology as the '685 application, and they also knew that Teva USA and its principal expert relied on a prior art reference that described the use of alendronate in beagles. Thus, the alleged inconsistency between Teva Ltd.'s use of beagles and Teva USA's criticism of Merck's beagle experiments was not a "revelation," but was apparent from evidence in the record created by those very attorneys. If the argument they make in their complaint in this case had any substance, Merck would have made it at the time.

Merck's lawyers' purpose in bringing this case is transparent: to delay the pending case between the parties. Indeed, as soon as they filed the complaint, Merck's lawyers sought a stay in that case. It is in Merck's economic interest to delay a resolution of the pending case as long as possible, since doing so accomplishes the dual purpose of keeping Teva USA out of the market and securing royalties under the patents in suit in that case.

Filing a bogus complaint is a serious matter, particularly when the filing is for the purpose of interfering with another pending case and the complaint publicly and falsely accuses lawyers of committing fraud on a federal court. In the case of a high profile litigation that implicates the public interest, such behavior is particularly egregious. A business entity depends on its reputation and goodwill. Likewise, for a lawyer, nothing is

more critical than his or her reputation. Merck had a responsibility not to use the Court system to try to trash the reputation of a competitor, and its lawyers had a responsibility not to attempt to trash the reputations of their adversaries by filing a baseless complaint falsely accusing them of fraud on the court. Merck's counsel who participated in this act, Mary B. Graham, John F. Lynch and Nicolas G. Barzoukas, should be personally sanctioned, as should their respective firms, Morris, Nichols, Arsht & Tunnel LLP, Howrey LLP and Weil, Gotshal & Manges LLP.

NATURE AND STAGE OF THE PROCEEDINGS

Merck filed its complaint in this case May 10, 2006. On May 31, 2006, Teva USA filed a motion under Fed. R. Civ. P. 12(b)(6) to dismiss the complaint for failure to state a claim upon which relief can be granted.

SUMMARY OF THE ARGUMENT

Merck's lawyers who are responsible for the complaint violated all three prohibitions of Fed. R. Civ. P. 11(b). First, they filed a complaint that was "not warranted by existing law." Fed. R. Civ. P. 11(b)(2). Merck's complaint purports to state a claim for relief under the "savings clause" of Fed. R. Civ. P. 60(b). That clause requires that, to reopen a judgment, the plaintiff must plead and prove a "fraud upon the court." Fed. R. Civ. P. 60(b). Merck's complaint makes no attempt to plead an actual fraud on the court. At best, it alleges a failure to provide discovery to Merck, which Merck's lawyers must know is insufficient to support a Rule 60(b) claim.

The complaint has no evidentiary support, and therefore was filed in violation of Rule 11(b)(3). Merck's lawyers here were involved in the case whose judgment they seek to reopen. They know that Teva USA did not conceal anything. In particular,

Merck's lawyers knew when they filed the complaint that, contrary to its allegations, Teva USA never agreed to, and specifically objected to, producing documents from its non-party parent corporation, Teva Ltd. In addition, as Merck's lawyers knew when they filed the complaint, Teva USA had objected to producing documents that did not relate to Teva USA's once-weekly alendronate product. Teva USA's objections are set forth in its responses to Merck's document requests, and Merck never challenged those objections.[1] The '685 application falls squarely within both of them.

Moreover, Merck's lawyers know that the "revelation" of the '685 application is at most duplicative of evidence that Merck already had. In particular, the trial and appeal record included another Teva Ltd. patent that with respect to beagles contains essentially the same disclosure as the '685 application. In addition, Merck's lawyers knew when they filed the complaint that Teva USA had actually relied on a prior art reference that described an experimental study in which beagles were treated with alendronate. Even though Merck's lawyers were aware of all this information, they never made the argument that Teva USA's criticisms of Merck's beagle experiments were "inconsistent" with Teva Ltd.'s employment of beagles. Thus, Merck's lawyers' allegations that the '685 application provided new and important impeachment information are false. By making the false factual assertions, Merck's lawyers violated Rule 11(b)(3).

Finally, Merck's lawyers brought the case for an improper purpose in violation of Rule 11(b)(1). Merck knows that it will probably lose the pending case between the parties. Every day's delay in the resolution of that case provides significant revenue for

[1] Merck's lawyers' bad faith is demonstrated by the fact that the complaint includes Merck's requests, but does not include Teva USA's responses.

Merck. By filing a complaint solely for the purpose of delay, Merck's lawyers have violated Rule 11(b)(1).

BACKGROUND

I. THE FOSAMAX ONCE-WEEKLY CASE

Merck is the owner of a patent family that claims the once-weekly administration of certain members of a class of drugs called "bisphosphonates." The drugs referred to in Merck's patents are prescribed for the treatment of bone disease. All of them were known as effective at the time Merck applied for the patent, so that the sole allegedly novel aspect that Merck claimed was the concept of administering the drugs on a less-frequently-than-daily basis, in particular once per week. One member of the family, U.S. Patent No. 5,994,329 ("the '329 patent") (D.I. 1, Ex. A), includes claims for the once-weekly administration of a drug called "alendronate" for the treatment and prevention of osteoporosis, a progressive and debilitating disease characterized by loss of bone mass and increased risk of fractures. Merck obtained the patent on November 30, 1999, based on an application filed in July 1997. The '329 patent protected Merck's once-weekly formulation of alendronate, which Merck has marketed as "Fosamax" since 2000.

In 2001, Teva USA supplemented an existing Abbreviated New Drug Application ("ANDA"). The supplement sought FDA approval to market Teva USA's generic version of the once-weekly Fosamax formulation, and included a certification that the '329 patent was invalid. Merck thereupon sued Teva USA in this Court. *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, No. 01-048 (JJF). The complaint alleged that the use of

Teva USA's proposed once-weekly alendronate product would infringe the '329 patent, and sought to enjoin Teva USA's marketing of that product.[2]

Teva USA conceded infringement, but defended primarily on the basis that the once-weekly administration of alendronate was anticipated by a prior art disclosure or would have been obvious in view of the prior art. Both parties' experts and all the inventors agreed that in 1997 persons skilled in the art would have understood that the claimed once-weekly regimen would be effective, and that it would have certain obvious advantages over the then-current once-daily formulation. To establish that this general understanding was published in the prior art, Teva USA relied on a publication called the *Lunar News*, which was a widely disseminated quarterly newsletter prepared by Dr. Richard Mazess, the president of a company called Lunar Corp., which manufactured equipment for measuring bone density. The evidence was undisputed that in July 1996, almost a year before Merck's invention date, a *Lunar News* article specifically suggested the once-weekly dosing of alendronate for osteoporosis, and recommended the appropriate dosage strength. Thus, all the essentials of the claimed invention were disclosed in one place.

In the face of the prior art, Merck tried a novel attack. Conceding that the reference disclosed the essentials of the invention, Merck argued that it should nevertheless be disregarded because the *Lunar News* was not a "peer-reviewed" publication and because its author, Dr. Mazess, did not have an M.D. or a Ph.D. degree in precisely the "right" field. Merck claimed that alendronate was known occasionally to

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[2] The procedural background is described in Judge Farnan's opinion. *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 288 F. Supp. 2d 601 (D. Del. 2003), *rev'd*, 395 F.3d 1364 (Fed. Cir.), *cert. denied*, No. 05-236, 2005 U.S. LEXIS 7831 (Oct. 17 2005). (D.I. 1, Ex. F.)

cause esophageal ulceration, so that increasing the dose from the daily level (10 mg) to the level necessary for once-weekly administration (70 mg) would have been counterintuitive to skilled medical practitioners. Thus, the suggestion from Dr. Mazess and his publication would have been insufficient to persuade skilled practitioners to follow his advice.

Teva USA's counter to that argument was two-fold: (1) it was legally irrelevant, and (2) it was factually wrong. First, the argument was irrelevant because whether a person skilled in the art would have been skeptical of the prior art has no bearing on the legal effect of that prior art. Thus, if the prior art teaches a patented invention, it is immaterial what the reaction of others would have been to it.

Second, Teva USA pointed out that the '329 patent itself did not include any clinical or other data showing any unexpected benefits of the once-weekly dose. The only experimental data in the patent was a report on a series of experiments on beagles reported in Example 1. These experiments involved anesthetizing beagles, bathing their immobilized esophagi in corrosive solutions of alendronate at various intervals, killing the dogs, dissecting their esophagi, and observing the damage caused by the solution.

At the trial of the action, Merck's witnesses made very little of these dog studies. Its principal expert, Dr. Socrates Papapoulos, never mentioned them in his testimony. (Ex. A at 627-711.)[3] Merck's esophageal expert, Dr. Fennerty, conceded that nothing in the studies was "directly relevant" to human experience. (Ex. A at 314.) Even the author of the study, Merck veterinarian Dr. Peter, admitted that the study did not have "any bearing on whatsoever on the clinical situation in which people take alendronate

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[3] Portions of the trial transcript are collected as Exhibit A.

sodium." (Ex. A at 210.) Merck's post-trial brief did not mention the studies, and its post-trial findings of fact referred to them only as providing the inspiration to the Merck inventors, but did not suggest that they had any independent relevance to the issues in the case. The district court made little of the dog studies; Judge Farnan's opinion mentions them only in passing: "Merck also undertook internal studies to understand the problem, including dog studies." 288 F. Supp. 2d at 624. (D.I. 1, Ex. F at 624.)

Although Judge Farnan did not rely on the Merck dog experiments, he did accept Merck's argument that doctors would have been skeptical of the *Lunar News* article and would not have been inclined to follow its lead. In view of that skepticism, he held that the claimed invention would not have been obvious.

On appeal, although Teva USA asked the court to overturn certain factual findings, its principal argument was not that Judge Farnan got the skepticism facts wrong, but instead that this skepticism was legally irrelevant. That is, even accepting Judge Farnan's factual finding that doctors would have been skeptical of the *Lunar News*, the claims were invalid. Teva USA argued that no legal basis exists for disregarding prior art merely because it would invite skepticism. Indeed, some of the greatest innovations in history have been made by people with the "wrong" backgrounds, and were consequently greeted with initial skepticism.[4] Thus, adding a prestigious and credible name to an old concept does not make it patentable.

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[4] The Wright brothers were bicycle mechanics when they invented the airplane, and Albert Einstein was an examiner in the Swiss Patent Office when he conceived the theory of relativity and the famous equation $E=mc^2$. Their discoveries were initially not credited in part because of their alleged lack of qualifications.

The Court of Appeals accepted Teva USA's argument. As it succinctly stated:

> Indeed, to the extent the district court finds Merck's weekly-dosing idea non-obvious because it went against prevailing wisdom, the court still must explain why Merck and not Dr. Mazess should get credit for the idea. Because Merck's idea added nothing to what came before, the district court's answer comes down to nothing more than the credentials of the authors. In this case that difference is not enough to avoid invalidating the claims.

395 F.3d at 1375. (D.I. 1, Ex. I at 1375.) In passing, the Federal Circuit mentioned what Merck conceded: the patent contains no human, animal or clinical data demonstrating the effectiveness of the claimed regimen. It thus adds nothing to the art that was not already set forth in the *Lunar News*. With respect to the dog studies, the court noted that they had been "discredited at trial" (*id.* at 1374), certainly a fair assessment in view of the testimony of Merck's own experts that the experiments had no relevance to human experience. Nevertheless, in context, it is clear that the focus of the Federal Circuit's opinion was its view that skepticism of the prior art is not a relevant consideration, as long as the prior art makes the invention obvious and enables its practice.

In its opinion, the Federal Circuit also addressed the construction of the term "about," which appears in the asserted claims. *Id.* at 1369-72. The meaning of "about" had been an issue at trial because Teva USA contended that if "about" meant "approximately," then the *Lunar News* would actually anticipate, that is, identically disclose, the claimed invention. On the other hand, if "about" meant "exactly," as Merck contended, then the disclosure would not anticipate the claims, but would nevertheless make them obvious. The district court had sided with Merck on this issue, but the Federal Circuit disagreed. Although its opinion devotes significant space to the claim construction question, ultimately the court noted that the strength of the reference was

such that even under Merck's and the district court's proposed construction, the result would have been the same. *Id.* at 1373 n.10.[5] Merck sought rehearing en banc. The full court denied the petition, and Merck then filed a petition for a writ of certiorari, which the Supreme Court denied.

II. TEVA USA DID NOT "CONCEAL" THE '685 APPLICATION DURING DISCOVERY

During the more than two years the district court case was pending before trial, the parties exchanged more than 100,000 documents and took 34 depositions. Ten different lawyers from two law firms appeared for Merck. Merck's efforts were also aided by a large and sophisticated patent department.

Early in the discovery phase, Merck served a set of document requests on Teva USA seeking information on a wide variety of topics, many of which, in Teva USA's view, were irrelevant. Merck directed its requests to a non-existent entity, "Teva," which it "defined" as including the corporate entity Teva Ltd. Teva Ltd. is an Israeli company, and is itself a large pharmaceutical manufacturer and innovator. It is the corporate parent of Teva USA, but was never named as a defendant, and was never served with any sort of process.

Since Teva Ltd. was not a party and had no interest in or involvement with the products at issue, Teva USA objected to Merck's so-called definition. Teva USA's responses make that objection explicit, stating that the definition was:

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[5] Judge Rader dissented from the majority's claim construction methodology and conclusion. Unlike the majority, he believed that the patent set forth a definition of "about" that was contrary to its ordinary meaning of "approximately." Nevertheless, Judge Rader's opinion nowhere states that he dissented from the ultimate conclusion: that the claimed invention would have been obvious under either construction.

> overly broad to the extent it includes entities beyond Teva Pharmaceuticals, USA. For purposes of the document request, responsive documents in the possession, custody or control of Teva Pharmaceuticals, USA will be produced.

(Ex. B hereto (Teva USA's responses to Merck's requests) at 5.) When Merck's lawyers filed the complaint in this action, they included the requests as an exhibit (D.I. 1, Ex. B), but omitted the responses. Those responses completely gut Merck's concealment contentions. This glaring omission was no accident. By itself it amounts to a false representation of fact.

At no time did Merck challenge Teva USA's objection to seeking documents from its corporate parent. At all times, Merck knew that no search would be conducted of Teva Ltd., and that documents would not be forthcoming from that entity. Indeed, Merck must have been aware that Teva USA meant what it said, since in fact no such documents were ever produced.

Although Merck knew of the absence of a connection between Teva USA's product and Teva Ltd., it also knew that Teva Ltd. had its own alendronate development program. Merck had sued Teva Ltd. separately in other countries. Indeed, prior to the trial of the '329 patent, Merck's case against Teva Ltd. on the corresponding British patent was tried in the British High Court of Justice, and Nicolas Barzoukas, listed as "of counsel" on Merck's complaint here, attended that trial.[6] Thus, if Merck was interested in exploring Teva Ltd.'s alendronate efforts, it would not have accepted Teva USA's

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[6] The High Court held the patent invalid, as has every other tribunal that has considered it, including the Federal Circuit, the European Patent Office, and the Federal Court of Australia. Teva USA contended that certain High Court findings of fact should be binding on Merck, but Judge Farnan declined to accord them collateral estoppel effect. 288 F. Supp. 2d at 611-12. (D.I. 1, Ex. F at 611-12.)

objection, and would have pressed for disclosure from Teva Ltd., either informally or by seeking relief from the Court. Merck did neither.

According to Merck, the key request was number 49. (D.I. 1 at ¶ 20.) That request states:

> All documents and things relating to research and development of alendronate and alendronate formulations or any other pharmaceutically active bisphosphonate and its formulations.

Teva USA believed that this request was much broader than warranted, and responded by objecting to the scope of the request and making absolutely clear that the scope of its response would be limited to the product actually at issue – Teva USA's weekly alendronate formulation:

> Teva [USA] objects to this request to the extent it is overly broad and unduly burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to the General Objections, responsive documents relating to the weekly alendronate product which is the subject of ANDA No. 75-710 will be produced to the extent they are relevant to the issues in this lawsuit.

(Ex. B at 24). Again, Merck's complaint quotes the request but omits the response. Again, this act cannot be other than a deliberate deception. At no time did Merck raise any issue with the limitation Teva USA had placed on its commitment to provide document discovery. Again, if Merck had been interested in further discovery, it could have pressed for it. It did not.

Thus, Teva USA placed two limitations on what it was prepared to produce: it would not seek documents within the custody and control of Teva Ltd., and it would not seek documents dealing with subjects other than the ANDA and ANDA products. Teva USA believed that these limitations were reasonable in light of the specifics of the case.

If Merck disagreed, it was free to challenge Teva USA's position, either formally or informally, but never did so.

The only discovery dispute involving Teva USA's document production arose not from Teva USA's decisions to limit its undertaking to provide discovery, but instead from Merck's contention that Teva USA had not sufficiently searched its own (not Teva Ltd.'s) files for documents relating to its own (not Teva Ltd.'s) products and development work. This issue culminated in Merck's filing a motion to compel. (Ex. C hereto.) The text of the motion makes clear Merck's complaint: that Teva USA had not sufficiently searched its own files and questioned its own employees. Nothing in that motion hints that Merck was in any way dissatisfied with the scope of the undertaking. Moreover, the motion nowhere mentions request 49, which is the centerpiece of Merck's concealment contention. It nowhere mentions Teva USA's objection to the overbroad definition of "Teva," and it nowhere mentions Teva USA's limitation to the ANDA products and their development. Instead, Merck's motion makes clear that Merck's only complaint was Teva USA's execution within the parameters of its own commitment.

Teva USA obviated the motion by conducting further searches for documents within Teva USA. (D.I. 1, Ex. C.) At no time did represent that it would gather documents from Teva Ltd., and at no time did it represent that it would search for documents beyond those relating to products other than those that were the subject of the ANDA. Nowhere in its complaint does Merck allege that Teva USA did anything less than what it expressly stated it would do or had done. Nowhere does Merck recite any facts to support its allegation that the letter from Teva USA's counsel is in any way not true.

Teva USA made timely objections to Merck's discovery requests and acted within the scope of those objections. If Merck was unsatisfied, it had the right to seek redress. *Clinchfield Railroad Co. v. Lynch,* 700 F.2d 126, 132 n.10 (4th Cir. 1983) ("Once a party registers, by way of a timely response, an objection to a discovery request, 'the initiative rests with the party seeking their production to move for an order compelling it.'") (citations omitted). To complain about Teva USA's responses several years after trial is absurd; to accuse Teva USA and its counsel of fraud for acting in accordance with those responses is reprehensible.

III. THE ALLEGED "REVELATION" OF TEVA LTD.'S BEAGLE EXPERIMENTS WAS IN THE TRIAL RECORD

A. Teva Ltd.'s U.S. Patent No. 6,476,006, Merck's Trial Exhibit 301, Discloses the Same "Beagle Study" as the '685 Application

The bankruptcy of Merck's lawyers' complaint is demonstrated by the fact that the allegedly "inconsistent" position of Teva USA was already part of the record, yet Merck made nothing of it during the trial, in post-trial briefing, on appeal, or in the Supreme Court. First, although Merck claims that it was a "revelation" that Teva Ltd. used beagles in its '685 application (D.I. 1 at ¶ 44), the district court record in fact includes another Teva Ltd. patent that contains the same information. In particular, after trial Merck moved to add to the record U.S. Patent No. 6,476,006 ("the '006 patent"), which had issued to Teva Ltd. (The '006 patent is Exhibit A to D.I. 1, Ex. K.) At the time it moved to add the patent, Merck claimed that it had just discovered it, even though it had been published a year earlier.[7]

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[7] Merck's assertion that it had just discovered the patent is wildly implausible. Alendronate is Merck's flagship product. It is not conceivable that Merck does not (continued...)

The '006 patent does not claim a new drug; instead, it is directed to a particular tablet construction that can be used with a number of drugs, including alendronate. Merck seized on an ambiguous sentence in the patent specification, which, according to Merck, suggests that the deleterious effects of alendronate are dose-related, a position that, again, according to Merck, was inconsistent with certain arguments Teva USA made at trial. Judge Farnan granted Merck's motion and the '006 patent was added to the record.

In all its discussion of the '006 patent, Merck never mentioned that it contains as Example 13 a report of a study involving beagles. In the study, the dogs were administered the claimed tablets, their urine was collected, and the bioavailability (area under the curve or "AUC") determined:

> Tablets from example 11 were administered to 3 beagle dogs in a crossover design versus an immediate release alendronate formulation. Urine samples were collected for 48 hours and an overall AUC for alendronate was determined.

(D.I. 1, Ex. K at Ex. A, col. 14, ll. 16-24.) The study design is essentially identical to that discussed in the '685 application, whose "withholding" is the basis for Merck's complaint. Merck's lawyers thus knew at the time that the '006 patent describes a bioavailability study carried out by Teva Ltd. that is essentially identical to the study described in the '685 application that Merck says was concealed. The very argument that Merck's lawyers say was made possible for the first time by the "revelation" of the '685 application was in fact available to them all along. Those lawyers never made that argument. Instead, Merck's lawyers discussed other aspects of the '006 patent, but never

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review every patent or other publication related to that product, and that it did not review this one as well.

mentioned the disclosure that they now say would have won the case for them. Thus, Merck's entire premise set forth in its complaint is false. Merck's lawyers knew when they filed the complaint in this case that the '685 application was not a "revelation," but instead was in all material respects equivalent to evidence in the record: (1) a patent document, (2) owned by Teva Ltd., (3) that revealed that Teva Ltd. had conducted bioequivalence studies using alendronate and beagles.

B. Teva USA and its Principal Trial Expert Relied on a Beagle Study

In addition to the '006 patent's disclosure of Teva Ltd.'s employment of beagles, as Merck's lawyers know, Teva USA actually relied on a prior art reference entirely focused on a study employing beagles. Initially, Merck asserted claim 1 of the '329 patent, which claimed "inhibiting bone resorption in a mammal" by administering alendronate on a less often than daily basis. Teva USA contended that a prior publication (the "Reddy article," Ex. D hereto), which included a discussion of a pre-clinical alendronate study involving beagles (which, of course, are mammals), anticipated claim 1. The title of the Reddy article could not have been more descriptive: *Alendronate Treatment of Naturally Occurring Periodontitis in Beagle Dogs*. Teva USA's principal expert, Dr. Russell, relied on this reference in his expert report. (The relevant portion is Ex. E hereto.) His deposition was taken by Nicolas Barzoukas, who asked no questions about the Reddy article. Shortly thereafter, Merck dropped claim 1 from the case. At trial, Dr. Russell was Teva USA's principal critic of the Merck patent data relating to its beagle study. He was cross-examined about his opinions of the Merck beagle data by Merck's lead trial counsel, John Lynch, who is also listed as "of counsel" in the complaint in this case. Mr. Lynch never questioned Dr. Russell about the Reddy article. Again, if there were any substance to the argument that reliance on beagle data was

inconsistent with criticism of Merck's beagle studies, Merck's counsel would have seized upon it at the time. In light of this episode, neither Mr. Barzoukas's nor Mr. Lynch's association with the complaint in this case is in good faith.

C. Teva USA's Trial Contentions Are Not Inconsistent with the '685 Application

The reason Merck's lawyers did not make the argument they are making now is that it was specious, and Merck's lawyers knew it then. The '329 beagle study has nothing to do with the studies recorded in the '685 application and the '006 patent. The Merck study was directed at injury caused by prolonged contact of esophageal tissues. In the study, beagles were first anesthetized. While they were immobile, solutions of alendronate were poured down their throats and allowed to remain in contact with their esophagi for a half hour. This dosing was carried out at different intervals (once per day, twice per week, etc.). Each dog was killed after the last dose, and its esophagus dissected and examined microscopically. (D.I. 1, Ex. A, col. 14, l. 10-col. 17, l. 20.) Teva USA's principal criticism of the study was that it did not model human clinical experience, and therefore was not germane to what happened to patients who actually took the drug. Merck's experts agreed with this assessment.

The study described in the '685 application (and in the '006 patent that Merck had) is fundamentally different. It is a bioequivalence study, not a study of tissue damage. In it, the beagles were dosed with the study drug and the concentration of the drug in their urine was measured. (D.I. 1, Ex. J at 8-11.) The fact that both studies involved beagles does not make them the same study, and Merck's lawyers know it. Again, if they had thought that the studies were equivalent, the had the opportunity to and

would have brought up the apparent inconsistency of Teva USA criticizing Merck's experiments at the same time its parent corporation was relying on its own beagle data.

The "inconsistency" argument was frivolous, which is why Merck never made it. It has not become less frivolous with the passage of time. Merck's lawyers' allegations that Teva USA concealed the pertinent evidence that would have turned the case around are childishly false.

IV. THE PENDING ONCE-WEEKLY RISEDRONATE CASE

In 2004, Teva USA filed an ANDA seeking permission to market a generic version of the once-weekly dosage form of another bisphosphonate, a drug called "risedronate." Like alendronate, it is indicated for the treatment of bone disease, in particular osteoporosis. Risedronate, however, is not a Merck product; it is instead marketed by Proctor & Gamble ("P&G") as "Actonel."

Although Actonel is not Merck's drug, the '329 patent and others in the same patent family include claims directed to the once-weekly administration of risedronate. Merck has therefore licensed the patents to P&G. (D.I. 1, ¶ 37.) The royalty rate is modest considering the expansive claims Merck makes for the invention, but Actonel once-weekly sales are huge, and Merck collects substantial revenues in royalties from P&G every month.

When Teva USA filed its ANDA for risedronate, it certified that the claims of the Merck patents that covered risedronate are invalid. Merck, as the owner of those patents, sued to enforce them. The parties have completed all fact and virtually all expert discovery and are preparing for trial, which is scheduled for August 28, 2006. Because essentially the same issues arise in both cases, the parties are employing for the most part the same expert witnesses and relying on the same or similar arguments. Of course, in

the alendronate case, Teva USA's arguments prevailed, and Teva USA believes that certain findings from that case are entitled to preclusive effect in risedronate case. Moreover, Merck must realize that having lost as a matter of law on its theory in the other case, it is unlikely to win here.

The claims Merck are asserting do not protect any Merck product. Merck, however, has a vital stake in their continued existence. First, as long as they are not held invalid, they guarantee the continued receipt of monthly royalties from P&G. As soon as they are declared invalid, P&G will stop paying royalties, thus permanently derailing Merck's gravy train. Second, Merck and P&G compete in the marketplace, but they do not compete on price. The entry of Teva USA's low-priced generic risedronate, however, would change that balance. Doctors would prescribe Teva USA's risedronate product instead of Merck's high-priced Fosamax, and Merck's Fosamax profits would plummet. Merck therefore has every reason not to go to trial, since it knows that the risedronate once-weekly claims will probably suffer the same fate as the claims of the '329 patent. That is why Merck has brought this action – not because it has any chance of overturning the Federal Circuit's judgment because of undisclosed beagles, but because every month's delay means millions more dollars for Merck.

To further its delay strategy, Merck's complaint asserts that Teva USA concealed the '685 patent in connection with the pending risedronate case, and that Merck is therefore entitled to more discovery on it. As they did with respect to the alendronate discovery requests, Merck's lawyers attached the discovery requests but inexcusably omitted the responses. (D.I. 1, Ex. M.) Merck falsely implies that Teva USA represented that it would produce documents from Teva Ltd. in that case, and deceptively omits that

Teva USA made it abundantly clear that it would not do so. In addition, Teva USA made it clear that its production was limited to documents relating to the development of its ANDA product. (Teva USA's responses are Ex. B hereto.) Again, not even Merck contends that the '685 application has any connection with that product.

Moreover, as discussed above, Merck's lawyers have had the '006 patent and the Reddy article for years, and if anything in them is inconsistent with the argument of Teva USA or its experts, Merck and its own experts would long ago have said so. Merck's experts in the pending case, Dr. Papapoulos and Dr. Fennerty, "reserved the right to supplement" their expert reports, but neither did so in light of Merck's "discovery" of this allegedly crucial document. In short, Merck's allegations, made by Mr. Lynch, Mr. Barzoukas, and Ms. Graham, are demonstrably false and without any reasonable basis.

V. MERCK'S LAWYERS KNEW THAT THE ALLEGATIONS IN THE COMPLAINT ARE FALSE

All the lawyers listed on the complaint were closely familiar with the record and with the evidence. Mary B. Graham signed virtually every pleading and motion in the case and attended the trial. John F. Lynch was lead trial counsel and argued the appeal. Nicolas G. Barzoukas was in charge of most of the pretrial conduct of the case and participated in the trial and appeal. All these lawyers are charged with a duty to investigate the facts.

ARGUMENT

Rule 11(b) provides in relevant part that:

> By presenting to the court (whether by signing, filing, submitting or later advocating) a pleading, written motion, or other paper, an attorney . . . is certifying that to the best of the person's knowledge, information, information, and belief, formed after inquiry reasonable under the circumstances, –
>
> (1) it is not being presented for any improper purpose, such as to harass or to cause any unnecessary delay or needless increase in the cost of litigation;
>
> (2) the claims, defenses, and other legal contentions therein are warranted by existing law or by a nonfrivolous argument for the extension, modification, or reversal of existing law or the establishment of new law;
>
> (3) the allegations and other factual contentions have evidentiary support or, if specifically so identified, are likely to have evidentiary support after a reasonable opportunity for further investigation or discovery....

Fed. R. Civ. P. 11(b). Rule 11 requires on "any party who signs a pleading . . . an affirmative duty to conduct a reasonable inquiry into the facts and law before filing." *Lony v. E.I. DuPont de Nemours & Co.*, 935 F.2d 604, 616 (3d Cir. 1991) (citations omitted). The Rule 11 standard is objective, so that protestations of subjective good faith are irrelevant if the pleading is "without factual foundation." *Id.* The purpose of the rule is to "discourage plaintiffs from bringing baseless actions or making frivolous motions." *Doering v. Union County Board of Chosen Freeholders*, 857 F.2d 191, 194 (3d Cir. 1988) (citations omitted).

I. MERCK'S LAWYERS FILED A COMPLAINT "NOT WARRANTED BY EXISTING LAW"

In filing the complaint, Merck's lawyers violated each of the three subdivisions of Rule 11(b). Taking them out of order, and starting with subdivision (2), Merck's

complaint seeks to reopen a judgment. Fed. R. Civ. P. 60(b) makes clear that an action can be brought to reopen a judgment more than a year old, as the judgment in this case is, only for "fraud on the court."

The case law makes clear that to prevail in such an action, the plaintiff must plead and prove that (1) an intentional fraud, (2) by an officer of the court, (3) which is directed to the court, and (4) that in fact deceives the court. *Herring v. United States*, 424 F.3d 384, 390 (3d Cir. 2005). Thus, although the complaint does not specify any such fraud, by bringing it, Merck's lawyers are saying that counsel for Teva USA defrauded the Federal Circuit, and that absent the fraud, the Federal Circuit would not have reversed the district court.

The sole allegation of "fraud on the court" is the alleged concealment of the '685 application. First, Merck's lawyers know that this allegation, even if true, cannot support Merck's claim. All the case law construing the savings clause makes clear that the fraud on the court rule means a fraud that interferes with the court process itself. For example, bribing a judge or a juror can be a fraud on the court. Manufacturing evidence can be a fraud on the court. In no way, however, can the non-disclosure of evidence to an opposing party rise to the level of a fraud on the court. Even if the allegations are true, Merck's complaint is baseless. Merck's lawyers have thus violated subsection (2), since they have not even attempted to meet the rigorous standard of Rule 60(b). A violation of subsection (2) by failing to make any effort to meet legal standards is sufficient to support sanctions under Rule 11. *See, e.g., Carlino v. Gloucester City High School*, No. 00-5262, 2002 App. LEXIS 17496, at *3 (3d Cir. Aug. 14, 2002).

II. MERCK'S LAWYERS FILED A COMPLAINT WITHOUT "EVIDENTIARY SUPPORT"

Merck's lawyers have violated subsection (3) by basing the complaint on allegations that not only do not "have evidentiary support," but are false. First, Merck's lawyers falsely characterized Teva USA's discovery obligations. The complaint they prepared deliberately and falsely omitted the two limitations those same lawyers had accepted: (1) Teva USA would not produce documents from Teva Ltd., and (2) Teva USA would not produce documents not relating to the development of its own once-weekly alendronate product.

Second, Merck's lawyers falsely characterized their discovery motion and Teva USA's response to that motion. The motion in fact recognized the limits on discovery of Teva USA, and only complained that Teva USA had failed to comply within those limits. Teva USA's lawyer's letter confirmed that Teva USA had made additional efforts to comply. Nothing in the record of either case even faintly suggests that the letter was not accurate in every respect. Merck's lawyers' cavalier statement that the letter was "false" itself is false and reckless.

Third, Merck's lawyers falsely state the relevance of the '685 application. They make the patently false argument that Teva Ltd.'s reliance in the '685 application on a bioavailability study that involved administering a drug to beagles and analyzing their urine is somehow inconsistent with any criticism of Merck's study that involved testing for esophageal damage by bathing the esophagi of immobilized beagles, and then killing and dissecting them. Merck's argument is silly, and none of its experts is willing to support it.

Fourth, Merck's lawyers falsely state that Merck's absurd argument was not available to them during the trial had they chosen to make it. Merck's lawyers know that the '006 patent, which was the subject of post-trial and appeal briefing, includes discussion of essentially the same methodology as the '685 application, yet those same lawyers did not mention that disclosure at the time. Merck's lawyers also know that long before trial Teva USA and its expert relied on a published study involving alendronate and beagles as anticipating claims of the '329 patent. The article includes both "alendronate" and "beagle" in its title.

Fifth, Merck's lawyers falsely state that the '685 application is relevant to the pending case on risedronate, a drug not discussed in connection with the beagle study in the '685 application. As before, when they took the deposition of Teva USA's principal expert, they knew of the '006 patent and the Reddy article, yet did not attempt to elicit testimony about the alleged inconsistencies it has since manufactured. Moreover, if Merck's lawyers thought that the document was relevant, they would have had their own experts supplement their reports to discuss it.

Merck's lawyers' violation of subsection (2) is especially egregious because the same lawyers represented Merck in the prior case. Their violation was therefore not merely a failure to investigate, but had to have been a deliberate deception, since they knew the record as well as anyone, and knew as they were drafting and signing the pleadings that they were making willfully false statements. In light of all these circumstances, the Court should impose sanctions on Merck's lawyers. *See Garr v. U.S. Healthcare, Inc.*, 22 F.3d 1274, 1281 (3d Cir. 1994) (affirming imposition of Rule 11 sanctions because lawyers did not make a "reasonable inquiry" before signing the

complaint); *Doering*, 857 F.2d at 193 (affirming imposition of sanctions "based on the filing of a frivolous complaint").

III. MERCK'S LAWYERS FILED THE COMPLAINT FOR AN "IMPROPER PURPOSE"

Finally, Merck's lawyers brought the complaint for a transparently improper purpose in violation of subsection (1). Merck's complaint is plainly for an illegitimate purpose – to delay the resolution of the pending case on risedronate. Since many of the arguments are the same in both cases, Merck knows that it is likely to lose. Such a loss will have profound economic consequences for Merck. In assisting Merck in its efforts illegitimately to avoid those consequences, its lawyers went way beyond the bounds of zealous advocacy.

* * *

CONCLUSION

Merck's lawyers, all of whom understood exactly what they were doing, have filed a complaint that alleges a fraud that they know did not occur. Their purpose in doing so is transparent: to delay and prejudice a pending case. Merck's lawyers and their firms should be sanctioned, and should at the least pay Teva USA's attorneys fees and costs.

YOUNG CONAWAY STARGATT & TAYLOR, LLP

June 5, 2006

Josy W. Ingersoll (No. 1088) [jingersoll@ycst.com]
Karen L. Pascale (No. 2903) [kpascale@ycst.com]
Adam W. Poff (#3990) [apoff@ycst.com]
The Brandywine Building
1000 West Street, 17th Floor
Wilmington, Delaware 19801
(302) 571-6600

Attorneys for Defendant,
Teva Pharmaceuticals USA, Inc.

OF COUNSEL:

James Galbraith
Maria Luisa Palmese
William G. James II
Huiya Wu
Colman B. Ragan
KENYON & KENYON LLP
One Broadway
New York, New York 10004
(212) 425-7200

EXHIBIT A

In The Matter Of:

Merck & Co., Inc. v.
Teva Pharmaceuticals USA

March 4, 2003

Federal Court Reporters
844 King Street
Wilmington, DE 19801
(302) 573-6195

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Page 1

IN THE UNITED STATES DISTRICT COURT
IN AND FOR THE DISTRICT OF DELAWARE
MERCK & CO., INC.)
) Volume 1
Plaintiff,)
) Civil Action
v.) No. 01-048 (JJF)
TEVA PHARMACEUTICALS USA, INC.)
Defendant.)
Tuesday, March 4, 2003
10:20 a.m.
844 King Street
Wilmington, Delaware
Courtroom 4B
BEFORE: THE HONORABLE JOSEPH J. FARNAN, JR.,
United States District Court Judge
APPEARANCES:
MORRIS, NICHOLS, ARSHT & TUNNELL
BY: MARY GRAHAM, ESQ.
-and-
HOWREY, SIMON, ARNOLD & WHITE
BY: JOHN F. LYNCH, ESQ.
NICOLAS G. BARZOUKAS, ESQ.
(Houston, Texas)
(Counsel for the Plaintiff)
YOUNG, CONAWAY, STARGATT & TAYLOR
BY: ANDREW W. POFF, ESQ.
-and-
KENYON & KENYON
BY: JAMES GALBRAITH, ESQ.
MARIA LUISA PALMESE, ESQ.
(New York, New York)
(Counsel for the Defendant)

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THE CLERK: All rise. (Whereupon Judge Farnan entered the courtroom.)

THE COURT: All right. Be seated, please.

Ready to proceed?

MS. GRAHAM: Yes.

MR. POFF: We're ready, Your Honor.

MR. LYNCH: Ready, Your Honor.

THE COURT: All right.

MR. LYNCH: Ready, Your Honor.

THE COURT: All right.

MR. POFF: Good morning, Your Honor. Adam Poff from Young Conaway on behalf of Teva. I'd just like to introduce from the firm of Kenyon & Kenyon, James Galbraith.

MR. GALBRAITH: Good morning, Your Honor.

MR. POFF: And Maria Palmese.

MS. PALMESE: Good morning, Your Honor.

THE COURT: Good morning.

MR. POFF: I'll turn the floor to Mr. Galbraith to make a few more introductions.

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MR. GALBRAITH: Before we start, I'd like to introduce representatives of our client that are here today. General counsel of Teva Pharmaceuticals, U.S.A., Mr. Richard Egosi is here. He just stepped out, but he'll be back.

Director of legal affairs of Teva U.S.A., David Stark, and the head of the patent department at Teva, Limited, the parent company, Dr. Yehudah.

THE COURT: Good morning.

MR. GALBRAITH: Your Honor, before we start the substance of the case, there are a couple of issues that I'd just like to talk about, more housekeeping matters.

The last trial we had and the subject matter, I believe, That Your Honor's procedure with respect to documents, documentary exhibits is that if there was an objection to a documentary exhibit, that we would reserve that and that — and it would be briefed, if necessary.

And I was wondering if that was Your Honor's procedure in this case.

THE COURT: Yes. You can use

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documents freely, and then just for the record, interpose the objection. And then if it's maintained, it can be maintained in post-trial briefing. And then I'll make a ruling on it.

MR. GALBRAITH: All right. Very well, Your Honor.

The other matter, Your Honor, I'd just like to revisit is the use of depositions. We reviewed Your Honor's order that limited us, both sides to 50 pages.

THE COURT: Is that enough?

MR. GALBRAITH: It's really not for us, because we have the burdens here. A certain amount of our case comes out of the males of Merck, that Merck's case. We stipulated to infringement and Merck has withdrawn its willful infringement.

There's a lack of balance there. I understand Merck really has no objection.

THE COURT: How far do you want to push the envelope?

MR. GALBRAITH: Well, Your Honor, perhaps if we could revisit the issue at the end of the trial, we could give you a pretty good

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estimate.

THE COURT: What I don't want to do is get stuck with a lot of citations in the post-trial briefing, and then because they're loosely done almost out of a security instinct, and then I wind up reading a lot of stuff that's cumulative, or sometimes it appears to be an unimportant detail.

But I don't want to prejudice any party from being able to designate deposition testimony that they truly need.

MR. GALBRAITH: Very well. Perhaps if it's all right with the Court, we could revisit this issue towards the end of trial when we have a better idea what the evidence looks like.

THE COURT: All right.

MR. GALBRAITH: Thank you, Your Honor. I appreciate that.

MS. GRAHAM: Your Honor, if I might just introduce my co-counsel and reintroduce my co-counsel before Mr. Galbraith starts his opening, John Lynch.

MR. LYNCH: Good morning, Your

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Honor.

MS. GRAHAM: And Nick Barzoukas of Howrey Simon. And Mr. Lynch will be making the opening statement today.

THE COURT: All right. Thank you.

MR. GALBRAITH: Thank you, Your Honor.

Your Honor, this is a — the case here is Merck & Company versus Teva Pharmaceuticals, U.S.A., and who, of course, we're representing the defendants Teva Pharmaceuticals, U.S.A.

And this case involves a single patent. It started out involving a number of patents, but now it involves a single patent.

And sort of a single overarching issue, and it's worth — two claims of that patent are valid.

Now, the patent is directed to a drug which we've already litigated in this room. And the drug is called alendronate sodium. It's sold under the trade name Fosamax by Merck, and Teva is seeking approval to market that drug, and has run up against the Merck patent here.

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And the Merck patent that's at issue, the '329 patent, claims once weekly administration of alendronate sodium for the treatment and prevention of osteoporosis. It doesn't claim a new drug. It doesn't claim a new indication.

It doesn't claim a new treatment. It is not an advance in medicine or science. It is simply a new way of dosing the drug, or an allegedly new way of dosing the drug. Taking it once a week, rather than seven times a week. Taking it on Saturdays rather than taking it on Monday through Sunday.

That's all it is. It's just an extension. It's just a dosing way of taking the drug, just a new way of taking the drug according to Merck.

Now, prior to this patent, and this is the prior art, it's part of the prior art. Alendronate sodium was a marketed product by Merck. It was previously marketed as Fosamax for the treatm-

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A: By microscopic examination.

Q: And were these dogs — these dogs, they were asleep and they were lying horizontal?

A: Yes.

Q: And the experiment just filled up their esophagi with alendronate solutions?

A: Yes. That's how the experiments are described.

Q: Now, do people lie horizontally when they take alendronate?

A: No, they're advised not to.

Q: And do people generally allow alendronate solutions to sit in their esophagi for 30 minutes?

A: No.

Q: And do the dog studies report any test of the inhibition of bone resorption?

A: No, they don't.

Q: And do these dogs have osteoporosis as far as the record shows?

A: No, they didn't.

Q: And did the dog studies address the non-serious GI effects that were discussed in, for example, in the Chestnut paper, nausea,

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dyspepsia, dysphasia, and things like that?

A: No. That's not possible to do in dogs.

Q: Do you have an opinion whether these dog studies are relevant to the clinical use of alendronate in people?

A: I do have a view. Yes.

Q: What is that view?

A: That they're not relevant.

Q: And maybe you could just explain why they're not relevant.

A: Well, given the experimental design, it doesn't simulate for what happens in real life. These are rather extreme and contrive experiments that were able to show that there were effects from alendronate, but under conditions that were unreal related to real life.

Q: Have you reviewed the testimony of the author of the dog studies, that is, Dr. — Merck's doctor, Dr. Peter?

A: Yes, I have.

Q: And let me Reid you a deposition excerpt from Dr. Peter. If we could put up Dr. Peter's deposition.

This is a deposition. This is an

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excerpt from the deposition testimony of Dr. Peter starting on Page 65.

"QUESTION: Well, generally, studies, well-performed studies enable you to predict something scientifically; correct?

ANSWER: Yes.

QUESTION: And do you think these studies, the doing studies allow someone to predict anything?

ANSWER: Not predict. These studies were done to look at the — look why and how these adverse effects are occurring in people.

QUESTION: So you don't think these studies are predictive?"

Any way getting down to an answer about what predictive means, a question at the bottom of the page:

"QUESTION: So the study was not designed to predict what would happen in patients?

ANSWER: No." Do you agree with Dr. Peter's characterization that the studies were not

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designed — couldn't be designed to predict what would happen in patients.

A: Yes.

Q: Could we turn to Page 83 of Dr. Peter's deposition, please.

"QUESTION: I'm trying to figure out whether you believe these dog studies have any bearing whatsoever on the clinical situation in which people take alendronate sodium.

ANSWER: That was not the purpose of these studies."

Does Dr. Peter's characterization of the studies seem reasonable to you.

A: Yes, it does seem reasonable.

Q: If I could take just a second.

(Following a discussion held off the record.)

MR. GALBRAITH: I have no further questions.

THE COURT: All right. Thank you.

CROSS-EXAMINATION

BY MR. LYNCH:

Q: Good afternoon, Dr. Russell.

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A: Good afternoon.

Q: Would you agree that the dog esophagus is a reasonable model for a human esophagus?

A: Not necessarily, no.

Q: So it is not even a model — that is, the doing esophagal mucous membrane is not a reasonable model for what you will encounter in a human?

A: No. The — may I answer this in more than one sentence?

Q: Yes.

A: I mean, the dog esophagus, as I understand it, has a structure that is similar to the human, but I think in terms of the appropriateness of the model, that is something.

Q: I just asked — but let's talk about the tissue. Isn't it true that the tissue, the dog esophagus itself is a reasonable model for a human esophagus; right?

A: Well, to that extent, the way that's described, yes.

Q: Okay. Now, and you did know that Dr. Peter's studies were published in a peer review journal; correct?

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A: Yes.

Q: So they were worthwhile studies that had a purpose in science; correct?

A: They have a purpose in science.

Q: And that purpose would yield someone's knowledge about how alendronate might behave if the alendronate were in contact with the type of tissue that is in the human esophagus for a long period of time; correct?

A: What they tell you is the potential for alendronate-induced damage.

Q: Yes.

A: But —

Q: In a human; correct?

A: No, in a dog.

Q: Oh, and it doesn't give you any information at all about what would be —

A: It may inform you about the mechanism of esophagitis, which is, as we've acknowledged, an extremely rare event in that it tells you how alendronate might irritate the mucosa. But you have to contrive the conditions under which you make that study by exposing them for much longer than the average patient would be exposed to when

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they take alendronate tablets.

Q: And what the dog studies kind of did, if I can summarize them in layman's terms, said if I put a smaller dose in on repeated days, put it in the dog on a number of individual days for a period of time, I wind up getting more irritation or more damage to this mucosal membrane than I would get by putting a multiple of the dose in every four days, or five days, or whatever it was; correct?

A: Well, with respect — that is actually not what you can legitimately

In The Matter Of:

Merck & Co., Inc. v.
Teva Pharmaceuticals USA

Trial Volume Number 2
March 5, 2003

Hawkins Reporting Service
715 N. King Street, Suite 3
Wilmington, DE 19801
(302) 658-6697 FAX: (302) 658-8418

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IN THE UNITED STATES DISTRICT COURT
IN AND FOR THE DISTRICT OF DELAWARE

MERCK & CO., INC.)
) Volume 2
Plaintiff,)
) Civil Action
v.) No. 01-048 (JJF)
TEVA PHARMACEUTICALS USA, INC.)
Defendant.)

Wednesday, March 5, 2003
9:30 a.m.
844 King Street
Wilmington, Delaware
Courtroom 4B

BEFORE: THE HONORABLE JOSEPH J. FARNAN, JR.,
United States District Court Judge

APPEARANCES:

MORRIS, NICHOLS, ARSHT & TUNNELL
BY: MARY GRAHAM, ESQ.
-and-
HOWREY, SIMON, ARNOLD & WHITE
BY: JOHN F. LYNCH, ESQ.
NICOLAS G. BARZOUKAS, ESQ.
(Houston, Texas)
(Counsel for the Plaintiff)

YOUNG, CONAWAY, STARGATT & TAYLOR
BY: ANDREW W. POFF, ESQ.
-and-
KENYON & KENYON
BY: JAMES GALBRAITH, ESQ.
MARIA LUISA PALMESE, ESQ.
(New York, New York)
(Counsel for the Defendant)

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THE CLERK: All rise. (Whereupon Judge Farnan entered the courtroom.)

THE COURT: All right. Good morning.

Be seated, please.

MR. BARZOUKAS: Good morning, Your Honor. If you recall, we had a scheduling issue.

THE COURT: Yes.

MR. BARZOUKAS: And with Teva's permission, without having concluded Dr. Russell's cross-examination, Merck is going to call Dr. Michael Brian Fennerty.

THE CLERK: Yes. Please state and spell your full name for the record, please.

THE WITNESS: Michael Brian Fennerty. M-I-C-H-A-E-L B-R-I-A-N F-E-N-N-E-R-T-Y.

THE CLERK: Please place your left hand on the Bible and raise your right hand.

MICHAEL B. FENNERTY, M.D., the witness herein, having first been duly sworn on oath, was examined and

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testified as follows:

DIRECT EXAMINATION

BY MR. BARZOUKAS:

Q: Good morning, Dr. Fennerty.

A: Good morning.

Q: Could you tell us where you're currently employed?

A: I'm a professor of medicine at Oregon Health Sciences University in Portland, Oregon.

Q: And what do your duties at the health sciences center involve?

A: It involves a clinical practice, seeing patients, teaching, research and administration duties.

Q: And do you currently have a medical practice, also?

A: I do.

Q: And what does your medical practice involve?

A: Medical practice seeing — involves seeing patients with general gastrointestinal disorders, and in a consultative format. Most of my consultative work and referral basis is in

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gastrointestinal disease of the esophagus and the stomach.

Q: Were you also engaged in this practice during the period between 1996 and 1997?

A: Yes, I was.

Q: And could you give us a brief description of your clinical practice during that period?

A: Clinical practice during that period was identical to what I had just stated, both gastroenterology with the focus in the upper gastrointestinal tract, purely as a consultative practice.

Q: And in your practice, what type of patients do you see?

A: I see a variety of patients from all aspects of diseases, related to the gastrointestinal tract, but mainly focused on diseases of the esophagus and the stomach.

Q: Do you also conduct research?

A: Yes, I do.

Q: And what does your research pertain to?

A: Most of my research pertains to diseases of the esophagus and the stomach specifically gastroesophageal reflux disease.

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Q: Dr. Fennerty, if you could give us a brief description of your educational background?

A: I graduated from the State University of New York at Albany in 1976. From medical school in Creighton University in Omaha Nebraska in 1980. Finished my residency in the United States Navy in 1984.

Did a fellowship from 1987 to 1989 in gastroenterology in the Department of Internal Medicine, University of Arizona Health Services Center, in Tucson, Arizona. And I stayed on faculty there before moving to Oregon.

Q: Dr. Fennerty, do you belong to any editorial boards?

A: Yes, I'm an editor, associate editor on the Editorial Board of, approximately, 10 to 12 medical journals almost exclusively gastroenterology related.

Q: Could you perhaps explain to us some of the most important journals on which you're — for which you're on their editorial board?

A: I'm on the editorial board for or the associate editor of the American Journal of Gastroenterology.

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And I also sit on the editorial board of the Archives of Internal Medicine, as well as a number of other journals pertaining to gastroenterology such as Gastrointestinal Endoscopy, and others.

Q: Do you also belong to any medical societies?

A: I belong to all four of the major gastroenterological societies. The American Association of Gastroenterology, American College of Gastroenterology, and the American Society for Gastrointestinal Endoscopy.

And I sit on a number of committees or governing boards of those three societies.

Q: Dr. Fennerty, do you have any publications?

A: Yes, I do.

Q: And have you written articles relating to gastroenterology?

A: Yes, I have.

Q: And could you tell us, approximately, how many?

A: It's, approximately, 250 papers, abstracts, and book chapters pertaining to

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gastroenterology that I've published or coauthored.

MR. BARZOUKAS: Your Honor, Merck would like to offer Mr. Fennerty as an expert in gastroenterology.

MR. GALBRAITH: No objection.

THE COURT: All right.

BY MR. BARZOUKAS:

Q: Dr. Fennerty, could you give us a brief description of the GI tract?

A: The gastrointestinal tract really encompasses everything between the esophagus of the swallowing tube down through the stomach, the small intestine to the large intestine, or the colon. But also involves the liver system and the pancreas as well.

Q: And can you perhaps concentrate

A: I think they're very, very inconvenient to patients, yes.

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Q: And so because they're very inconvenient, doing it every day, is it fair to say that it's reasonable, a reasonable expectation would have been that a weekly that patients would comply better with a weekly regimen?

A: I think that that is a very accurate statement, yes.

Q: And they would comply better in the sense that they would stay with the drug longer and they would also comply better in the sense that they would comply with the specific instructions better; is that right?

A: Especially the latter, I think.

Q: Now, the dog studies that you testified about that are in the patent, just so we're clear, they don't model the human experience; is that right?

A: I'm not sure what you mean by model. They clearly are not reflective of what happens in the human, but they are a model of esophageal injury related to bisphosphonates and alendronate.

Q: Well, in a human experience, the severe injury from use of taking daily bisphosphonates

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is a very unusual occurrence; correct?

A: It's unusual, yes.

Q: And so this model, this dog model doesn't model the human experience with alendronate; isn't that correct?

A: It doesn't — it's not directly reflective of what happens physiologically, but I'm not sure I understand what you mean by the term "model".

Q: Well, let's look at your deposition. Go to Page 146 of day one.

Okay. On Page 146, which I'll put up on the screen.

First of all, do you recall having your deposition taken a couple months ago in this case?

A: I do.

Q: And if we could look at the questions beginning at Line 11. It says:

QUESTION: Okay. But in the human experience, the severe injury to the esophagus is a very unusual occurrence; correct?

ANSWER: That's correct.

MR. BARZOUKAS: Could I ask, Your

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Honor, for the witness to get a copy of this?

MR. GALBRAITH: Sure. I'll give him my copy.

BY MR. GALBRAITH:

Q: Would you like it?

A: Please.

Q: Yeah. Here's my copy.

So, QUESTION: This model doesn't so this doesn't model the human experience with alendronate; is that correct?

ANSWER: Not at all.

Is that THE testimony that you gave at that time, Doctor.

A: That's correct, in reading through the transcript.

Q: And these dog studies have nothing to do with the tolerability of the drug in terms of the kinds of side effects that resulted in the withdrawal of patients from the Chestnut study; is that right?

A: Well, the dog study, they didn't measure nausea, vomiting abdominal pain, which were the adverse events requiring all of the Chestnut study. That's correct.

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Q: And the dog studies wouldn't support the safety of alendronate once a week, would they?

A: Well, potentially, yes. I think that not at all is taken out of the context of the questioning at the time. If that's what you're asking me.

Q: No, that's not what I'm asking.

The results of the experiments wouldn't support the safety of the use of alendronate on a once-weekly basis; is that correct, although it may lead one to hypothesize?

A: That's correct.

Q: It's another piece of information that would make you reconsider your concerns of higher doses on a frequent or infrequent basis; right?

A: There are hypotheses generating in the studies.

Q: And the study has no data that's relevant to the human experience; is that right?

A: Not directly relevant, no.

MR. GALBRAITH: If I may have a moment, Your Honor.

(Following a discussion held off the record:)

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MR. GALBRAITH: I have no further questions.

THE COURT: All right.

MR. BARZOUKAS: Your Honor, I just have a couple very quick questions.

THE COURT: Sure.

REDIRECT EXAMINATION

BY MR. BARZOUKAS:

Q: Doctor, you mentioned MRL, could you, for clarity of the record, explain what you mean by MRL?

A: It refers to Merck Research Laboratories, which is their research and development arm for the company, at least as I know it to be.

Q: And the only other thing I want to ask you is if you would go to Exhibit 138 that's before you.

A: Yes.

Q: And ask you if you could read the date that that article was published?

A: Yes. As I mentioned this is quite a bit later than the other publication. This is May of 1998.

Q: And that's the Peter study on rats?

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A: That's correct.

MR. BARZOUKAS: Your Honor, no more questions.

MR. GALBRAITH: I just want to get my stuff back together.

THE COURT: Okay. Thank you, Doctor.

MR. BARZOUKAS: Your Honor, may the witness be excused, because he has to catch a plane later this afternoon?

MR. GALBRAITH: Sure.

THE COURT: You have no further question?

MR. GALBRAITH: I have nothing further. Thank you.

THE COURT: Okay. You're excused, Doctor.

THE COURT: We'll take a 15-minute recess.

THE CLERK: All rise.

(A brief recess was taken.)

THE CLERK: All rise.

(Whereupon Judge Farnan entered the courtroom.)

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THE COURT: All right. Be seated, please.

MR. LYNCH: May it please the Court, we're ready to continue with the cross-examination of Dr. Russell.

THE COURT: Okay. Dr. Russell, will you retake the witness stand, please, sir?

THE WITNESS: Good morning.

THE COURT: Good morning.

BY MR. LYNCH:

Q: Good morning, Dr. Russell.

A: Good morning, Mr. Lynch.

In The Matter Of:

Merck & Co., Inc. v.
Teva Pharmaceuticals USA

Trial Volume Number 3
March 6, 2003

Hawkins Reporting Service
715 N. King Street, Suite 3
Wilmington, DE 19801
(302) 658-6697 FAX: (302) 658-8418

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IN THE UNITED STATES DISTRICT COURT
IN AND FOR THE DISTRICT OF DELAWARE
MERCK & CO., INC.)
) Volume 3
Plaintiff,)
) Civil Action
v.) No. 01-048 (JJF)
TEVA PHARMACEUTICALS USA, INC.)
Defendant.)
Thursday, March 6, 2003
9:30 a.m.
844 King Street
Wilmington, Delaware
Courtroom 4B
BEFORE: THE HONORABLE JOSEPH J. FARNAN, JR.,
United States District Court Judge
APPEARANCES:
MORRIS, NICHOLS, ARSHT & TUNNELL
BY: MARY GRAHAM, ESQ.
-and-
HOWREY, SIMON, ARNOLD & WHITE
BY: JOHN F. LYNCH, ESQ.
NICOLAS G. BARZOUKAS, ESQ.
(Houston, Texas)
(Counsel for the Plaintiff)
YOUNG, CONAWAY, STARGATT & TAYLOR
BY: ANDREW W. POFF, ESQ.
-and-
KENYON & KENYON
BY: JAMES GALBRAITH, ESQ.
MARIA LUISA PALMESE, ESQ.
(New York, New York)
(Counsel for the Defendant)

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THE CLERK: All rise.

(Whereupon Judge Farnan entered the courtroom.)

THE COURT: All right. Be seated, please.

BY MR. LYNCH:

Q: Good morning, Dr. Yates.

A: Good morning.

Q: Dr. Yates, let's move forward now more directly to your making of the invention that's the subject of the patent here in this suit.

When did this occur? When did you first start beginning to appreciate the potential value of once-weekly dosing?

A: It was in May of 1996.

Q: And what were the — what was the occasion on which this happened?

A: This was a discussion that occurred between Dr. Art Santora, who worked in my group and myself following the initial understanding of the results of the dog studies that we conducted to better evaluate the mechanism of the esophagitis.

Q: And do you have in front of you the —

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yes, the book with the material. Are those dog studies that appear in the patent in suit?

A: Yes. These are the same dog studies that were quoted in the patent, yes.

Q: And which ones are they that you received in May of 1996?

A: In particular, this was the — the studies that revealed that single dosing with alendronate at 0.2 milligrams per mill had no impact on the dog's esophagus, but that repeated exposure at five times daily to alendronate 0.2 milligrams a mill in acid was associated with ulceration of the esophagus in this dog model.

Q: Turn to the patent, please. The '329 patent at Column 16.

A: Which tab is this under?

Q: One. PTX 1.

A: PTX 1.

Q: There it is. It's on the screen.

A: Yeah.

Q: I just wanted to ask you, which of the experiments in Table 1, if any, were the experiments that you got in May of 1996?

A: This was the groups that are one and two

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that are shown here.

Q: That's Group 1?

A: Group 1, the animals having the no alendronate, but having an acid solution given daily for five days.

And Group 2, the animals that received alendronate 0.2 milligrams daily for five days showing the difference in the impact of the these treatments on the dog's esophagus.

Q: And did you have another experiment run at that time that involved a single exposure?

A: That's — that's correct. The first studies that were done were to look at single exposure of alendronate at 0.2 milligrams per mill. And in those studies, even at acid Ph, when the animals were examined after the exposure, there was no damage to the esophagus.

So it was a combination of the fact that we did see damage after repeated exposure, and that we had not seen any damage after single exposure that first suggested to myself and Dr. Santora that a single dosing may be a way of treating individuals and having a significant amount of esophageal irritation.

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Q: Now, what was the stimulus for conducting these dog studies in the first place?

A: The dog studies were conducted to further explore the mechanisms of esophageal damage that we had seen, and subsequently were reported in the de Groen paper.

Q: Now, what was the status of your work in the de Groen paper around this time, let's say, around May and earlier in 1966?

A: In March of 1966, Dr. De Groen had contacted Merck with the — to discuss the cases that he had seen that are subsequently reported in his publication, and we worked with Dr. De Groen throughout March and April and into May of 1996 to further characterize the clinical situation, including the full exploration of all of the cases that we had observed adverse events reported to us that related to the esophagus.

Q: Now, and just explain what was involved with respect to Merck and Dr. De Groen at this time.

A: All right. Dr. Daifotis and I had extensive discussions with Dr. De Groen to understand the characteristics of the cases that

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he subsequently reported with us in the New England Journal.

We invited Dr. De Groen and some other experts in gastrointestinal disease to a meeting very, quickly organized meeting at Merck in March 15th. So about two weeks after our first understanding that these cases existed, to evaluate all of the information that we had available to us at that time.

Q: How seriously was this being taken at the time?

A: Extremely serious.

Q: What was the upshot of what happened with your meetings with Dr. De Groen and everything else? Just let's carry this forward through March and April.

What was going on?

A: Right. In the March 15th meeting, there was a lot of discussion about the individual cases that we had observed. The cases that, some of which were suggestive of a pill esophagitis, i.e., potentially a tablet sticking within the esophagus and causing local damage, and others that were suggestive of acid reflux being the

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primary cause of the problem.

And we had also discussed with the consultants the mechanisms that — how dosing may relate to the risks of esophageal damage in both of these scenarios, and that's how we determined the changes to the product labeling and recommendations to physicians and patients that subsequently we took forward.

Q: Now, what did you do then? What was your response to this issue?

[2] A: Yes.

[3] Q: And there's a section entitled Safety And [4] Tolerability Studies of Humans.

[5] A: Yes.

[6] Q: And down at the bottom of that, there's a [7] sentence that begins Convincing human [8] tolerability data for a higher dose of [9] alendronate comes from clinical trials of [10] alendronate and the treatment of Paget's disease.

[11] Do you see that?

[12] A: Yes. Convincing human tolerability.

[13] Q: And do you agree with that statement?

[14] A: To read it again, it says convincing [15] human tolerability data for a higher dose of [16] alendronate come from clinical trials of [17] alendronate in the treatment of Paget's disease, [18] and in as much as it reflects to Paget's patients [19] who are, after all, humans, then it is a true [20] statement.

[21] Q: Well, the context of this was showing [22] support in the clinical world for your efforts to [23] go ahead with the weekly administration of [24] alendronate for osteoporosis; correct?

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[1] A: Yes.

[2] Q: And so —

[3] A: And so it is one part of the overall [4] discussion within this paper.

[5] Q: And just so we're clear, the references [6] we go to — if we go to the — into that [7] discussion, there's a series of references 12, 13 [8] and 56.

[9] Do you see that?

[10] A: Can I — can I draw your attention before [11] we go there to the same paragraph that you drew [12] my attention to before human intolerability — [13] studies in — Safety and Tolerability studies in [14] Humans on page ending 123?

[15] Q: Whatever you like.

[16] A: Two pages back.

[17] Q: Okay.

[18] A: The column two, the paragraph at the top [19] right-hand side here, we are talking about safety [20] and tolerability studies in humans, and we also [21] provide the counter balancing information within [22] this paper by bone, despite the fact it's a [23] rationale paper, about the experience with 40 [24] milligrams, then we go on to describe the results

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[1] from the Chestnut paper and the fact that about [2] ten percent of patients developed upper GI [3] symptoms that resulted in discontinuation where [4] discontinuation is were less common at lower [5] daily doses, 5 to 20 milligrams, or with placebo.

[6] So I think it is appropriate to read [7] all of this information in context, and we are [8] not simply stating that the Paget's studies on [9] their own are convincing, we are saying that [10] those data provide convincing data that in [11] humans, which is true that alendronate can be [12] well tolerated, but we go on to say in patients [13] with osteoporosis, even doses of 40 milligrams [14] may be associated with a discontinuation is due [15] to upper gastrointestinal events.

[16] Q: But nevertheless you do refer to the [17] purpose of the paper is to talk about the likely [18] tolerability of a once weekly dose for [19] alendronate; correct?

[20] A: Right. And the paper is wide ranging and [21] discusses a number of pieces of evidence that [22] when considered together, provides support for [23] the concept.

[24] Q: And the references that are after the

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[1] little section on convincing human tolerability [2] that we discussed, those are the Siris, Reid, and [3] Kahn studies; correct?

[4] A: Yes, and Cummings is also — not [5] Cummings, rather, the Chestnut paper.

[6] Q: I was just referring to the ones we were [7] talking about, the Paget's experience.

[8] A: Yes. I understand, and I was for [9] completeness indicating that we have been [10] complete and referenced the Chestnut paper, also.

[11] Q: Generally, after the de Groen paper or [12] these case reports started to come out about the [13] severe, the rare severe occurrences of [14] esophagitis, and even after the de Groen paper [15] came out, the acceptance of Fosamax in the [16] marketplace continued to climb; correct?

[17] A: Yes. The event clearly had an effect on [18] our overall potential trajectory, but [19] nonetheless, the sales of Fosamax which at that [20] time was relatively early on post-launch, did [21] continue to increase.

[22] Q: And they increased rapidly; correct?

[23] A: Yes. I would say, however, that because [24] of the concerns and awareness about GI

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[1] tolerability, that it's likely although [2] impossible to prove, that they would have been [3] more rapid had we not seen these adverse events.

[4] Q: That's speculation. The fact of the [5] matter is they did increase rapidly; correct?

[6] A: Yes, and I think they also —

[7] MR. GALBRAITH: Thanks; I have no [8] further questions.

[9] THE COURT: All right.

[10] MR. LYNCH: One question.

[12] REDIRECT EXAMINATION

[13] BY MR. LYNCH:

[14] Q: There was some suggestion about the [15] Lufkin paper and the dosing on the Lufkin paper. [16] Do you have PTX 87? I don't think it's in that [17] book that counsel gave you.

[18] A: PTX 87?

[19] Q: Yes.

[20] A: I have 83 and 89.

[21] Q: Did counsel give you the Lufkin paper?

[22] A: Oh, yes, I have that.

[23] Q: And go to page 322 on the Lufkin paper in [24] the left-hand column near the bottom. What does

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[1] it say about the dosing procedures? Look at the [2] line begins "after our initial case of [3] esophagitis".

[4] A: "After our initial case of esophagitis, [5] all patients had been instructed to follow [6] procedures known to facilitate passage of tablets [7] through the esophagus, to take medication on an [8] empty stomach with eight ounces of water, and not [9] to recline for one hour."

[10] Q: Does that substantially reverse the [11] taken-at-bedtime instruction on page one?

[12] A: It does.

[13] MR. LYNCH: No further questions. [14] (The witness left the witness stand.)

[15] MR. LYNCH: May it please the Court, [16] Your Honor, Merck calls Dr. Socrates Papapoulos.

[17] THE CLERK: Please state and spell [18] your full name for the record. Socrates, [19] S-O-C-R-A-T-E-S; Papapoulos, P-A-P-A-P-O-U-L-O-S.

[21] DIRECT EXAMINATION

[22] BY MR. LYNCH:

[23] Q: What is your current professional [24] position, Dr. Papapoulos?

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[1] A: I'm a professor of medicine, and a [2] consulting physician and director of bone and [3] mineral research in the department of [4] endocrinology and metabolic diseases at the [5] Leiden University Medical Center.

[6] **Q:** Where is the Leiden — how do you spell [7] Leiden?

[8] **A:** L-E-I-D-E-N.

[9] **Q:** And where is the Leiden University [10] Medical Center?

[11] **A:** In the Netherlands.

[12] **Q:** In the Netherlands.

[13] And what is the nature of your [14] position there? I mean, what are your duties and [15] responsibilities?

[16] **A:** I do have clinical research, teaching, [17] and administrative duties.

[18] **Q:** And in general, what does your — what do [19] your teaching and clinical responsibilities [20] involve? What particular aspect of the practice [21] of medicine? You are a medical doctor; correct?

[22] **A:** I am an internist and endocrinologist, [23] and my duties are exclusively in the field of [24] bone and mineral metabolism.

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[1] **Q:** Now, describe what is the nature of your [2] clinical experience as it's developed at Leiden [3] today?

[4] **A:** As it is today, or as it did develop?

[5] **Q:** No, today.

[6] **A:** Today my clinical duties include doing an [7] outpatient clinic, doing telephonic [8] consultations, doing a ward runs, and teaching [9] younger physicians in the management of problems [10] of bone and mineral metabolism, and at the same [11] time, consulting with other departments within [12] our university hospital, mainly gastroenterology, [13] renal diseases, orthopedics, and so on.

[14] **Q:** Now, Dr. Papapoulos, what is the status [15] or stature of the University of Leiden when it [16] comes to the practice of medicine involving bone [17] metabolic diseases?

[18] **A:** It is in the forefront of the European [19] centers as it's taken together with the [20] University of Aberdeen, University of Sheffield [21] in the UK, in Lee on in France, and the group in [22] Geneva in Switzerland. These are the places [23] where basic and clinical research in bone disease [24] has been conducted.

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[1] **Q:** And in general, what kind of patients do [2] you see in your clinical work?

[3] **A:** Any type of patient with any type of bone [4] disease.

[5] **Q:** Insofar as the subject matter of this [6] case is concerned, to what extent do you involve [7] yourself with the treatment of patients that have [8] either osteoporosis or Paget's disease?

[9] **A:** These are the most common patients that I [10] see in my clinic and also my colleagues see [11] within our group.

[12] For the Paget's disease, we are the [13] main referral center in the Netherlands, and we [14] have one of the largest Paget's populations in [15] the world.

[16] **Q:** Now, let's go on to a little bit of your [17] background, Dr. Papapoulos.

[18] Can you trace for me a little bit of [19] what your background is and your education, [20] medical school?

[21] **A:** Yes, I obtained my M.D. at the University [22] of Athens in Greece where I did also my training [23] in internal medicine.

[24] Then I moved to London where I spent

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[1] about six years at the Middlesex Hospital at the [2] University of London together with Jeffrey [3] O'Riordan, which is one of the well-known figures [4] in Britain in metabolism. I completed, and I [5] started conducting research in calcium and bone [6] metabolism.

[7] Are later on in 1984, I moved to [8] Leiden. When I joined the group of Professor [9] Olaf Bijvoet, whom I succeeded in leading this [10] group in 1999.

[11] **Q:** Now, at the time you joined the [12] University of Leiden, what was the status in the [13] area of treatment of these various bone metabolic [14] diseases?

[15] **A:** It was certainly in the frontline, [16] because Professor Olaf Bijvoet, apart from these [17] other achievements in this area, was the man who [18] had discovered pamidronate, and he was the first [19] to use it clinically.

[20] **Q:** Now, how many publications do you have, [21] Dr. Papapoulos, in the field of bone metabolic [22] medicine?

[23] **A:** About 300, excluding abstracts.

[24] **Q:** And what's societies, if any, do you

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[1] belong to that deal with this particular area?

[2] **A:** I belong to any major international [3] society dealing with bone and mineral metabolism. [4] But in addition to that, I am on the board of [5] directors of the IBMS, the society in which [6] Professor Russell was president three years ago. [7] And I'm also in the board of the International [8] Osteoporosis Foundation.

[9] This International Osteoporosis [10] Foundation is the largest organization dealing [11] with osteoporosis, and it has members societies, [12] scientific societies, and patient societies from [13] about 90 countries in the world.

[14] **Q:** And have you received any awards or [15] distinctions in this area of medicine?

[16] **A:** Yes.

[17] **Q:** Of bone metabolic disease?

[18] **A:** I have. I believe that relevant fo this [19] case is perhaps the Boy Frame Award of the [20] American Society for Bone and Mineral Research [21] for excellence in the clinical field of bone [22] metabolism, being the first non-American to [23] receive this award.

[24] **Q:** Now, Dr. Papapoulos, I'm going to direct

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[1] your attention to Exhibit 246 in this book, and [2] ask you what it is?

[3] **A:** Yes, this is my C.V.

[4] **Q:** And is this C.V. reasonably accurate [5] summary of your background and experience in the [6] area of bone and metabolic disease?

[7] **A:** I believe so.

[8] **MR. LYNCH:** I submit, Your Honor, [9] that Dr. Papapoulos is an expert in this [10] particular field of medicine.

[11] **MR. GALBRAITH:** No objection.

[12] **THE COURT:** All right.

[13] **BY MR. LYNCH:**

[14] **Q:** Dr. Papapoulos, you arrived in 1984 at [15] the University of Leiden. And I would like to [16] reflect back to then on this issue of Paget's [17] disease.

[18] **A:** Yes.

[19] **Q:** You arrive at the University of Leiden, [20] and I think that's far enough back.

[21] What's the status of what you're [22] doing with Paget's disease at that time?

[23] **A:** You mean therapeutically?

[24] **Q:** Therapeutically, yes.

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[1] **A:** We were treating patients with Paget's [2] disease with pamidronate at that time.

[3] **Q:** And what was the nature of the [4] pamidronate treatment you were administering to [5] Paget's disease patients at that time?

[6] **A:** By that time, we were treating giving [7] oral pamidronate to patients with Paget's disease [8] because of the GI problems, and we were [9] initiating treatment with intravenous drug.

[10] **Q:** So at this time, back in 1984, you were [11] experiencing these problems that were later [12] reflected in a '90s article by Lufkin that we [13] just looked at; is that fair to say?

[14] **A:** That is fair to say. However, the [15] experience with Lufkin was with a lower dose than [16] the dose used in Paget's disease.

[17] Q: Yes.

[18] Now, what, if anything — well, at [19] this time, 1984, when you were treating Paget's [20] disease, what were the doses you were using [21] orally, even if you replaced them because of [22] problems, and the doses you were using [23] intervenously?

[24] A: Right. Orally, the effective dose was

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[1] 600 milligrams per day, which as I said, it could [2] not be well tolerated.

[3] When we reduced it to 300 milligrams [4] a day, which could be tolerated, it was not so [5] effective.

[6] And so we moved to the intravenous [7] where we're using 20 to 30 milligrams [8] intervenously per day for three, four, five days, [9] or even longer sometimes.

[10] Q: Now, this intravenous administration, [11] what did it necessitate? How did you administer [12] this to the patient?

[13] A: So the patient was admitted to the [14] hospital, we were giving it by infusion usually [15] between two and four hour slow-running infusion.

[16] Q: At this point in time, you're treating [17] Paget's patients in the Netherlands with [18] pamidronate?

[19] A: Yes.

[20] Q: What is the Paget's treatment available [21] for patients in the United States?

[22] A: Sometimes the only available treatment in [23] the United States was oral etidronate. So no [24] other effective treatment was available to

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[1] American physicians.

[2] Q: And what about other things we've heard [3] about, like clodronate, as another material?

[4] A: Clodronate never been approved in the [5] United States; it's only approved in a few [6] countries in Europe. And so there weren't any [7] other bisphosphonates.

[8] In fact, to tell you an anecdote, at [9] that time, both in Sheffield and in our unit in [10] Leiden, patients from the United States with [11] Paget's disease were coming for treatment.

[12] Q: Because —

[13] A: Because of the non-availability of [14] effective treatments in the United States.

[15] Q: Now, let's talk about those people, what [16] is the nature of the — of the symptoms or the [17] nature of the people that you treated?

[18] A: Yeah.

[19] Q: Even beginning back in 1984.

[20] A: I don't have to go all back to 1984 [21] because the patient in the clinic with Paget's [22] disease is very typical. As a patient that comes [23] in and has complaints, the main complaints of [24] this patient is pain.

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[1] In 80 to 85 percent of patients with [2] Paget's in all clinical series reported up until [3] now, pain was a predominant symptom, and it is [4] the published experience of Professor Kanis from [5] Sheffield, and it is exactly the same without [6] published experience.

[7] Then we have other issues like [8] deformities, loss of hearing, because of [9] localization in the skull fractures in about 14 [10] percent of these patients.

[11] Q: Now, I think Dr. Russell said that only 5 [12] to 10 percent of Paget's patients had the pain [13] symptoms.

[14] A: Which is absolutely correct, but this is [15] a population, which is being seen in clinical [16] units. Only 10 percent of the population will [17] you see was without symptoms.

[18] The large majority were the [19] symptomatic patients.

[20] Q: So you're saying out in the world, there [21] might be people afflicted with Paget's, and only [22] 5 to 10 percent of them have pain?

[23] A: Oh, yes. Very much so.

[24] Because we heard Paget's disease is

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[1] common. It is three percent in people about the [2] age of 50 and 55 years old.

[3] So the majority of patients out [4] there without symptoms, you know, nobody knows [5] where they are.

[6] Q: But the people that you treat for Paget's [7] in your clinic —

[8] A: Yes.

[9] Q: And you're as well in Great Britain and [10] at Sheffield, I mean?

[11] A: No, I wasn't. I was at Sheffield in [12] London.

[13] Q: I mean, in London. Did you treat people [14] there?

[15] A: It's a very few, because it was not an [16] expertise, but we have a physician there who [17] follows them, who had particular interest in this [18] disease and would be seeing these patients.

[19] Q: Those patients, in the clinical setting, [20] they have pain?

[21] A: Yes. They were identical to the patients [22] I used to see.

[23] Q: Now, is that changing today? That is, to [24] what extent are unsymptomatic patients being —

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[1] for Paget's disease being treated today?

[2] A: Because during the past years, we have [3] obtained very efficacious and convenient ways of [4] treating Paget's disease. There has been a [5] general consensus during the past two or three [6] years to start treating patients without [7] symptoms, but with localizations of the disease [8] in places in the skeleton, which can induce [9] complications to treat them in a way [10] prophylactically.

[11] But this is a very recent [12] development due to their availability of [13] efficacious and safe ways of treating.

[14] Q: And what are those ways of treating them?

[15] A: Oral bisphosphonates.

[16] Q: Oral bisphosphonates. And which one do [17] you use?

[18] A: I do use oral resindronate in my practice [19] in daily practice now.

[20] Q: And resindronate is the product of?

[21] A: Alendronate.

[22] Q: And in the — in the Netherlands at the [23] present time, is alendronate approved —

[24] A: No.

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[1] Q: — for the treatment of patents?

[2] A: No. It is — alendronate 40-milligram [3] tablets are not available in the Netherlands.

[4] Q: But is alendronate used for the treatment [5] of osteoporosis?

[6] A: Certainly.

[7] Q: Now, let's go to your background in [8] insofar as these patients are concerned. These [9] Paget's patients were symptomatic with pain.

[10] Is this a disturbing pain that [11] motivates them to seek treatment?

[12] A: Oh, absolutely.

[13] Q: Could you describe it?

[14] A: This is a disturbing pain. Sometimes it [15] can be very bad. It can be excruciating.

[16] And particularly, when it is due [17] really to the bone disease, it is very prominent [18] at night. So patients wake up at night - at [19] night because of that pain.

[20] So it is a very, very specific [21] complaint.

[22] Q: Now, when you were offering the [23] treatments back then and the treatments today [24] with the oral bisphosphonates, generally, what's

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[1] the nature of the success rate you have of [2] overcoming this pain symptom

with the Paget's [3] disease patients?

[4] A: Bisphosphonates are great drugs in [5] relieving the pain in patients with Paget's [6] disease.

[7] Q: What is the — what is the progress of [8] the treatment —

[9] A: So —

[10] Q: — if you look at the symptomatic [11] Pagetic patient?

[12] A: So in my first discussion with the [13] patient in whom I have made the diagnosis of [14] Paget's disease, I explain to them what Paget's [15] disease is, what bisphosphonates are, and what [16] our expectations of this treatment.

[17] Namely, I say to the patient that [18] there is a great chance that within the period, [19] the short period you take the tablets, your pain [20] will go down and perhaps may disappear.

[21] The point is that the patient has to [22] understand that you're giving two to six months [23] treatments, giving two months treatment now with [24] resindronate. It's six months with alendronate.

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[1] And you say to the patient, you take [2] this treatment, your symptoms will ease down. [3] And then you will have a period of two, three, [4] four years perhaps without any treatment or any [5] new symptoms.

[6] Q: And you said two, three, four years,. [7] After that two, three, four years, is it typical [8] that there may be a relapse?

[9] A: Yes.

[10] Q: And —

[11] A: A relapse can occur. And it depends.

[12] There are patients who relapse after [13] one year. There are patients who relapse after [14] eight or nine years.

[15] Q: Let's get to the —

[16] THE COURT: Mr. Lynch, we're going [17] to take our lunch break now until 1:30.

[18] MR. LYNCH: Very good, Your Honor.

[19] THE COURT: I'm going to stay here. [20] I have a pretrial conference. You'll all free to [21] go.

[22] (A luncheon recess was taken.)

[23] THE CLERK: All rise.

[24] (Whereupon Judge Farnan entered the

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[1] courtroom.)

[2] THE COURT: All right. Be seated.

[3] MR. LYNCH: May it please the [4] Court.

[5] BY MR. LYNCH:

[6] Q: Good afternoon, Dr. Papapoulos?

[7] A: Good afternoon, Mr. Lynch.

[8] Q: Let's go on to osteoporosis; [9] Dr. Papapoulos.

[10] In 1984, when you got to Leiden, was [11] there a treatment for osteoporosis available at [12] that medical center?

[13] A: At that medical center, we used [14] pamidronate for the treatment of our patients [15] with osteoporosis.

[16] Q: Now, we've just heard that pamidronate [17] apparently was withdrawn from an approval process [18] in the United States as late as the '90s as a [19] result of the Lufkin article?

[20] A: Yes.

[21] Q: How was it that in 1984 in Leiden, you [22] were able to use pamidronate?

[23] A: Actually, we developed pamidronate, oral [24] pamidronate at 150 milligrams per day for the

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[1] management of osteoporosis. And on the basis of [2] the good results we had, Ciba-Geigy, who had the [3] license to these drugs — to this drug, in about [4] '89-'90 organized international trials.

[5] So we participated in that, the [6] Lufkin study. The Mayo Clinic participated in [7] the same study here in Reid, New England, [8] Dr. Fogelman, and Dr. Stevenson in the United [9] Kingdom,, and other centers in Denmark and in [10] Sweden. And during this trial, it was before the [11] publication of the Lufkin, we got a message from [12] Ciba-Geigy, that the trial should be interrupted [13] due to adverse events.

[14] Q: Could you put up Exhibit 67. Turn to —[15] I'm sorry, 87. Can you identify Exhibit 87, [16] Dr. Papapoulos?

[17] A: Yes. 86. 87.

[18] Yes. I have it.

[19] Q: And what is that document?

[20] A: Yeah. That's a famous article we have [21] been discussing.

[22] It's a Lufkin article talking about [23] the side effects, the event of adverse affects [24] that has been seen during this trial with

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[1] pamidronate.

[2] Q: Now, you were using pamidronate even [3] earlier than these trials; correct?

[4] A: Yes.

[5] Q: And was that with governmental [6] permission?

[7] A: That was with the permission in our [8] medical community.

[9] Q: And what was your experience with these [10] same types of adverse effects —

[11] A: Pamidronate.

[12] Q: — involving pamidronate?

[13] A: Yeah. Pamidronate, at that dose was a [14] pretty good treatment fo osteoporosis. It was [15] very good.

[16] Only 10 to 12 percent of the [17] patients receiving pamidronate could not tolerate [18] it. So seeing what we had at that time, [19] available for the management of osteoporosis, [20] this was great.

[21] It was very effective. It was [22] working in nearly 90 percent of the patients with [23] no problems.

[24] And it created problems to about 10

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[1] to 12 percent of the patients.

[2] Q: Now, when you saw a patient with problems [3] with pamidronate at this level you've just [4] indicated, what was the nature of those problems [5] that you saw?

[6] A: Many of the problems were epigastric [7] complaints, that is, pain. Abdominal pain. [8] Nausea. Vomiting. Heartburn.

[9] Q: So you were a part of this same trial [10] that's being reported to — reported on by [11] Lufkin?

[12] A: We were writing the similar study.

[13] Q: What did you do when that trial was [14] called off?

[15] A: We stopped giving Ciba-Geigy's [16] preparation of pamidronate, because we couldn't [17] go on. They withdrew all the samples. And we [18] continued the trial with our pamidronate.

[19] Q: And how long did that study last?

[20] A: Five years.

[21] Q: And what was the upshot of that study?

[22] A: It was a very effective treatment.

[23] Q: Now, during this time, you were treating [24] both Paget's patients —

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[1] A: Yeah.

[2] Q: — and osteoporosis patients?

[3] A: Yes.

[4] Q: How were you treating Paget's patients at [5] Leiden during the same period of time?

[6] A: With intravenous pamidronate or with [7] bisphosphonates which we were developing. I [8] mean, we were doing research development.

[9] Q: Now —

[10] A: Clinical practice was intravenous [11] pamidronate.

[12] Q: Why was it intravenous for the Paget's [13] patients and oral for the osteoporosis patients?

[14] A: Because it was a big difference in the [15] dose. The dose, which was effective in Paget's [16] disease was 600 milligrams per day. And this [17] could not be tolerated by the majority of these [18] patients.

[19] Q: And was there a dose that the Paget's [20] patients could tolerate that was higher than the [21] osteoporosis dose?

[22] A: 300 milligrams was well tolerated, but it [23] was not effective enough to treat the disease.

[24] Q: So, and is this in the general period of

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[1] the late '80s, earlier '90s? Could you summarize [2] what was your experience with the toleration that [3] osteoporosis patients had with oral pamidronate [4] as opposed to Pagetic patients?

[5] A: Patients with osteoporosis could tolerate [6] pretty well 150 milligrams per day. When it was [7] going to 300 milligrams, we have a placebo study [8] of that patient.

[9] There was a clear increase in the [10] incidence of side effects and dropouts.

[11] Q: Is that in osteoporosis?

[12] A: This was in rheumatoid arthritis, not on [13] osteoporosis. But it was a similar type of [14] patient, and there was three times higher dropout [15] due to GI side effects.

[16] Patients with Paget's disease could [17] not tolerate 600 milligrams. They could tolerate [18] 300 milligrams.

[19] And finally, patients with [20] metastatic bone disease, which is another [21] indication when we give bisphosphonates, could [22] not tolerate 600 milligrams, but were tolerating [23] 300 milligrams.

[24] Q: Now, you used the word of something that

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[1] I think the reporter missed, that is something [2] rheumatoid?

[3] A: Rheumatoid arthritis.

[4] Q: Now, do you have an explanation for that, [5] the different tolerance levels?

[6] A: No.

[7] Q: But —

[8] A: I mean, you can — there is — I don't [9] think anybody has an explanation for that, but [10] there are various issues, which are indicative, [11] you can say, of these differences.

[12] For example, it's at that time, our [13] typical patient with osteoporosis was the patient [14] who presented during your opening statements with [15] that particular slide, who has the little old [16] lady with this problem.

[17] That was our typical osteoporotic [18] patient, on the other hand. In the Paget's [19] population, we knew that men, predominantly a [20] little bit more, but it were more men than women.

[21] Secondly, we heard also yesterday [22] with Dr. Markowitz saying that women at that age [23] have a much higher incidence of GI problems than [24] men.

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[1] So if you put all this together, you [2] may come to some explanation. Finally, and I [3] think for me is the most important, the patient I [4] was seeing with Paget's disease, who had disease [5] had problems, had complaints, and I was offering [6] a treatment for that.

[7] In the lady with osteoporosis, what [8] I was telling her was, Look here. This is a [9] great drug. It's going to reduce your risk of [10] fracture in the coming years by about 50 percent.

[11] If we think also of the worst [12] scenario, the lady who already had experienced a [13] vertical fracture. She comes to me.

[14] What do I say? Look here. [15] The pain will go down by itself [16] within three months. The drug I'm giving you is [17] not going to have any effect on your pain, but [18] it's going to prevent fractures in the future.

[19] So I think without having any [20] scientific data, any scientific study, you know, [21] which has examined this issue specifically, I [22] believe that from clinical practice you can come [23] to this kind of differentiation between patients.

[24] Q: Now, let's move into the '90s. And in

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[1] the '90s, what do you use to treat — what do you [2] use currently to treat osteoporosis at the center [3] in Leiden?

[4] A: In my clinical practice, I'm using [5] alendronate.

[6] Q: And that's alendronate?

[7] A: Today's alendronate weekly.

[8] Q: Weekly. And before alendronate weekly [9] came along, what did you use?

[10] A: Alendronate daily.

[11] Q: What is generally the nature of your [12] experience that you have had in your clinical [13] practice with the appearance of these adverse [14] effects or adverse events with alendronate daily?

[15] A: Actually, I was not surprised at all [16] because the profile I was seeing in my clinic was [17] exactly the same to what I have seen before with [18] oral pamidronate.

[19] Q: Now, but, of course, pamidronate was at [20] 150 per day?

[21] A: Yes.

[22] Q: Correct?

[23] A: Yes.

[24] Q: And the alendronate was at 10 per day?

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[1] A: Yes.

[2] Q: And what were you seeing, just generally?

[3] A: You want me to explain why it was a [4] difference?

[5] Q: No. By what percentage of the people?

[6] A: It was about the same 10 to 12 percent of [7] the people were getting exactly the same kind of [8] complaints, and they were discontinuing treatment [9] because of that.

[10] I mean, the patient — it is very [11] typical, and I think it is very nice to read the [12] paper, but if you don't have the patient across [13] you saying, Doc, I can't. I have the pain. I [14] vomit.

[15] I can't take it. This is what [16] you're hearing from your patients.

[17] Q: Now, let's talk about the issue of what a [18] dose-related response is.

[19] A: Yes.

[20] Q: And do you have an opinion as to whether [21] bisphosphonates generally exhibited those [22] dose-related responses?

[23] A: You mean in terms of tolerability —

[24] Q: Tolerability.

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[1] A: — or efficacy.

[2] Q: In terms of tolerability.

[3] A: Yes, I do. Yes.

[4] I do have an opinion of that.

[5] Q: And what is it?

[6] A: That there is a clear dose-related [7] response.

[8] Q: And where — what do you base that on?

[9] A: First of all, let's start with the [10] earlier development bisphosphonates, which were [11] not so irritative of the gastrointestinal mucosa [12] nearly, etidronate and clodronate, and this has [13] been extensively discussed during the previous [14] two days.

[15] What we can summarize, and as been [16] shown in Dr. Fleisch's book, it was that these [17] two bisphosphonates exhibit mild gastrointestinal [18] disturbances. And when you reduce the dose or [19] you split the dose, these go away,.

[20] Or another way to deal with that is [21] to give the drug ihtravenously. When we

come to [22] the first amino bisphosphonate, namely [23] pamidronate, there is a very clear dose [24] relationship. And I have explained to you all

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[1] the issues involved in pamidronate.

[2] Then, we come to alendronate. And [3] as very rightly pointed before, we can't [4] extrapolate from one bisphosphonate to another. [5] However, alendronate had only one carbon more [6] than pamidronate.

[7] Otherwise, it was the same, but [8] surprisingly was much more potent.

[9] **Q:** Well, let's explore some of the other [10] common traits.

[11] When you gave pamidronate — when [12] you gave pamidronate intravenously, —

[13] **A:** Yes.

[14] **Q:** — what was the effect?

[15] **A:** During the first administration of the [16] drug, we had a very specific reaction of the [17] patient.

[18] **Q:** What's it called?

[19] **A:** Which is called acute phase reaction.

[20] **Q:** And what was the nature of an acute phase [21] reaction?

[22] **A:** Usually during — after the second day, [23] after the intravenous treatment, the patient was [24] getting high temperature, muscle aches.

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[1] This is a kind of flu-like syndrome, [2] which was associated with changes in its blood [3] count, which were transient.

[4] **Q:** So it didn't have a long effect, but you [5] felt like you had the flu for a couple of days?

[6] **A:** Yes. Severe flu.

[7] **Q:** What's the situation with intravenous [8] alendronate?

[9] **A:** When alendronate was introduced, and it [10] was given in the first place intravenously, [11] patients had, although in lower doses, patients [12] experienced exactly the same reaction.

[13] So the acute phase reaction as has [14] been described with pamidronate and which meant [15] that investigators using alendronate described [16] that very clearly.

[17] **Q:** Now, to what extent would those, in about [18] 1995/1996, to what extent did literature indicate [19] that there might be a dose-related response [20] insofar as gastrointestinal effects affecting [21] tolerability is concerned might exist with these [22] various bisphosphonates? And can you explain [23] with regard to the various articles summarized on [24] what is it, 13 or —

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[1] **A:** Which ones could you do you want me [2] specifically to focus on?

[3] **Q:** Are there any articles that illustrate [4] and report on a dose phase reaction?

[5] **A:** On an acute phase or dose related?

[6] **Q:** I mean a dose-related action. Here we're [7] talking about the gastrointestinal tract.

[8] **A:** Let's look at one publications. For [9] example, 77, British Medical Journal, 50 [10] milligrams a day, 50 percent problems.

[11] **Q:** Is that Harinck, PTX 77?

[12] **A:** '87. It's the last one.

[13] **Q:** And that was a paper which you were an [14] author?

[15] **A:** Yes.

[16] **Q:** What did it report?

[17] **A:** We reported on the effectiveness of these [18] regimens, and as you can see here, we had [19] problems with the 600 milligrams. When we gave [20] the 300 milligrams, we didn't have any problems.

[21] **Q:** So it wasn't a dose-related reaction with [22] pamidronate?

[23] **A:** And the disease for us was a very good [24] indication, and we state that.

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[1] **Q:** Any others?

[2] **A:** The second, again, with pamidronate, [3] comes from General Clinical Oncology, 1993, [4] van Holten. This is in patients with metastolic [5] bone disease where we had to change the dose to [6] 300 milligrams because patients could not [7] tolerate it.

[8] **Q:** That's PTX 84.

[9] **A:** Oh, yes.

[10] **Q:** And does that support the notion that [11] there is a dose-related reaction?

[12] **A:** For pamidronate, yes.

[13] **Q:** Any others?

[14] **A:** Can we go back? Before I go to the [15] Fleisch publications, let me go to the Adami [16] publications which is in Bone. Sadam Adami was [17] an Italian investigator which was perhaps the [18] first one who used in a proper way alendronate [19] before these became available to Merck.

[20] So he used two doses to treat [21] patients with Paget's disease, 20 and 40 [22] milligrams a day, patients with Paget's disease [23] who had never seen bisphosphonates before. And [24] he came to the conclusion that the 40 milligrams

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[1] were problematic for the patients, and he said [2] that probably in the future, we would not be able [3] to use oral alendronate for the management of [4] Paget's disease.

[5] You may say that this was perhaps [6] due to the preparations they were using, but this [7] is totally irrelevant, because there's a closed [8] dose-related effect independent of preparation [9] because patients tolerated much better the 20.

[10] **Q:** The 20 milligram dose was tolerated?

[11] **A:** Was tolerated.

[12] **Q:** That was the same preparation?

[13] **A:** Exactly. That's why I'm saying it has [14] nothing to do — it gives me an indication of [15] dose relationship.

[16] **Q:** Let's go now to alendronate specifically [17] in osteoporosis.

[18] **A:** I'll pick up the January 1995 Kanis in [19] Osteoporosis International.

[20] **Q:** That's PTX 115.

[21] **A:** Dr. Kanis, as we have discussed also [22] previously here, is a great expert in [23] bisphosphonate, the use of bisphosphonates, work [24] in Sheffield. He has used numerous of these

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[1] compounds, and here he is writing a review [2] article to position alendronate for the [3] management of osteoporosis.

[4] And as you can see, clearly, in his [5] conclusion, it says the problem, the only problem [6] is gastric intolerance, which is dose dependent.

[7] So if I am somebody who is not too [8] heavily involved in this area, and I read one of [9] the great experts in bisphosphonate treatment say [10] that, immediately, I take account of that.

[11] And then comes the book of [12] Dr. Fleisch. It was yesterday described as the [13] Bible, and Fleisch is the father of the [14] bisphosphonates. And his authoritative [15] monograph, he states that very clearly.

[16] **Q:** Dose dependency?

[17] **A:** Right.

[18] So I have perhaps the people who are [19] mostly respected in the field saying that, I have [20] my own personal experience with pamidronate, and [21] for the reasons I told you is very close to that.

[22] So therefore, what more I need? I [23] need a real study. And that was the Chestnut [24] study.

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[1] **Q:** And what is your conclusion based on the [2] Chestnut study?

[3] **A:** That it produces excess 40 milligrams [4] produces excess of GI side effects, leading to [5] discontinuation.

[6] **Q:** In what kind of patients?

[7] **A:** Patients with osteoporosis.

[8] **Q:** You've also seen the studies that were [9] done by Merck in connection with Paget's disease?

[10] **A:** Yes.

[11] **Q:** And how do you accommodate what happened [12] in the Chestnut study with what happened in those [13] Paget's studies?

[14] **A:** The only explanation I can offer to you [15] is what I said before about the patient with the [16] osteoporotic versus the patient with the Paget's [17] disease. And the patient who is osteoporotic, [18] with osteoporosis, is the most relevant for me.

[19] And this combined with all the data [20] I have, combined with my experience with [21] pamidronate being different in Paget's and in [22] osteoporosis, I come to the conclusion that [23] indeed, the 40 milligram per day dose is not [24] relevant for patients with osteoporosis.

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[1] **Q:** Dr. Papapoulos, refer, if you will, in [2] your book to Exhibit 124.

[3] **A:** Yes.

[4] **Q:** Is that a study or report on which you [5] are familiar?

[6] **A:** Yes, well, I would like more to keep the [7] word report rather than a study.

[8] **Q:** Okay, it's a report?

[9] **A:** Yes.

[10] **Q:** Why are you saying that?

[11] **A:** Because this was not a study of [12] scientific, great scientific value. This was a [13] study which went to look what's happening in [14] daily practice after the introduction of [15] alendronate.

[16] **Q:** What did Dr. Ettinger report was [17] happening in daily practice with alendronate?

[18] **A:** Many different things from what have [19] happened in clinical trials, which is the [20] experience of every single doctor who has worked [21] both as a clinical investigator and a practicing [22] clinician.

[23] So here, Dr. Ettinger found that a [24] big number of these patients, if I recall

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[1] correctly was about 18 percent, had to [2] discontinue treatment because of GI side effects, [3] which is more or less a little bit more [4] exaggerated than my experience, and I believe I [5] have a lower incidence because I know better how [6] to do bisphosphonates.

[7] **Q:** And this indicated 18 percent?

[8] **A:** About, yes.

[9] **Q:** In osteoporosis?

[10] **A:** Had to discontinue the study.

[11] So for me it is a clinical study [12] which confirms what every single clinician was [13] seeing in daily practice with the use of [14] alendronate.

[15] **Q:** Now, Dr. Papapoulos, let's go to the [16] Lunar News article.

[17] **A:** Can you point me out there where?

[18] **Q:** Yeah, I think we're somewhere around 28 [19] and 29, two the Lunar articles of April '96 and [20] July '96.

[21] **A:** Should I look in April '96?

[22] **Q:** No, let me ask you a question first about [23] is the Lunar News a publication that you were [24] familiar with back around this time frame in

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[1] 1995/1996?

[2] **A:** Yes, I was familiar with it.

[3] **Q:** And just tell me how you came to become [4] familiar with it?

[5] **A:** It was coming in my mail. I don't know [6] how I've been selected. I suppose they [7] distribute it out to many physicians.

[8] **Q:** And what was the — at the time that this [9] one arrived, do you have any recollection of the [10] weekly suggestion, whatever has been set forth, [11] whatever you want to call it, about weekly [12] administration of alendronate?

[13] **A:** No.

[14] **Q:** Now, have you since looked at these Lunar [15] News articles?

[16] **A:** At the articles, yes, in relation to this [17] litigation.

[18] **Q:** Do you have an opinion as to whether [19] these articles would tell a person like yourself [20] of skill in the art and be an effective teaching [21] of the same inventions as in the '329 patent for [22] the administration of alendronate for [23] osteoporosis treatment?

[24] **A:** Definitely not.

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[1] **Q:** Can you explain why?

[2] **A:** Because the suggestions that are here [3] made do not have any rationale. They don't have [4] any scientific basis. And the proposed [5] approaches are, do not fit with each other. [6] They're approaches which are based on very [7] different principals, as have been discussed [8] earlier. Weekly is different than giving once [9] weekly intravenously, one week a month, one week [10] every few months, every so and so.

[11] So I believe that anybody skilled in [12] the art and knowing bisphosphonates would [13] immediately discard these articles.

[14] Furthermore, now if we want to look [15] more seriously to what he's saying, one of the [16] main points he makes is that alendronate is not [17] tolerated by about 15 percent of the patients.

[18] So in order to address the issue of [19] convenience, side effects, and cost, he proposes [20] something.

[21] But he never addresses the issue of [22] side effects. Whatever he proposes, he doesn't [23] come to issues of side effects.

[24] **Q:** Are you talking about in April or in both

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[1] of them?

[2] **A:** I mean, the first is not pointing at that [3] at all. He's just thrown a suggestion. I'm [4] talking about the next article.

[5] **Q:** Let's go to the Exhibit 29, that's the [6] next article of Lunar News.

[7] **A:** July '96?

[8] **Q:** July 1996. That's Exhibit 29.

[9] Now, this is the one he says 40 and [10] 80 —

[11] **A:** Can you point me to the page here?

[12] **Q:** I wish I could.

[13] **A:** I think I found it for you, 23. Yep, [14] it's that. It's on the screen. We were both [15] looking here and it was on the screen.

[16] **Q:** This is the one that indicates in the [17] last paragraph in the middle column, even oral [18] alendronate could be given in a 40 or 80 [19] milligram dose once a week to avoid dosing [20] problems and reduce costs.

[21] **A:** Yes.

[22] **Q:** In your opinion, is that an effective [23] disclosure of the same invention comprised in the [24] '329 patent in the Lunar News?

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[1] **A:** No, for a very simple reason. He is [2] using 40 and 80 not on any scientific rationale, [3] but because it is available.

[4] Secondly, he doesn't tell us how [5] he's going to address the issue of side effects, [6] which is one of the main points in this [7] particular article.

[8] **Q:** Well, read on, he does —

[9] **A:** He goes on and says intravenous [10] administration. Because it was used at the time.

[11] Let me tell you what was happening [12] with all these suggestions of Dr. Mazess. One [13] week each month, etidronate was given once a [14] month, failed to show anti-fracture efficacy, [15] withdrawn from the market.

[16] Ibandronate, something that he [17]

suggests, given in intravenous injections every [18] three months in a proper trial with nearly 3,000 [19] patients over three years, no anti-fracture [20] evidence.

[21] So even if you want to say that he [22] has a point here, he doesn't have a point at all.

[23] **MR. LYNCH:** I have no further [24] questions, Your Honor.

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[1] **THE COURT:** All right.

[3] **CROSS-EXAMINATION**

[4] **BY MR. GALBRAITH:**

[5] **Q:** Doctor, do you have the Lunar News July [6] 1996 issue?

[7] **A:** Oh, I had it just now. I think it was — [8] 86?

[9] **MR. LYNCH:** It's 29, Doctor.

[10] **BY MR. GALBRAITH:**

[11] **Q:** It's Plaintiffs Exhibit 29.

[12] **A:** Yes, I have it.

[13] **Q:** And if we go to the relevant page —

[14] **A:** Twenty-three.

[15] **Q:** Twenty-three in this issue, and the part [16] we were just looking at, the last paragraph under [17] the column, now, he says, a suggestion there, he [18] says, " Even oral alendronate potentially could be [19] given in a 40 or 80 milligram dose once a week to [20] avoid dosing problems and reduce costs."

[21] **A:** Yes.

[22] **Q:** Now, if someone followed that suggestion [23] are and gave oral alendronate 80 milligrams once [24] a week to a patient, that would be a safe and

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[1] effective therapy for osteoporosis; correct?

[2] **A:** It would be an effective therapy for [3] osteoporosis. Whether it could be a safe [4] therapy, I don't know, and the data pointed to me [5] it's most probably not going to be a safe [6] therapy.

[7] **Q:** We know 70 milligrams is a safe therapy?

[8] **A:** Now?

[9] **Q:** Yes.

[10] **A:** I'm sorry. I didn't understand your [11] question. Do you want me to put myself from the [12] present position to '96?

[13] **Q:** Let me ask you again. I'm not asking [14] you what you might have thought. If in fact [15] somebody did that today, picked up this Lunar [16] News and followed that suggestion and dosed 80 [17] milligrams a week to an osteoporotic patient, [18] that would be a safe and effective therapy for [19] osteoporosis; correct?

[20] **A:** You mean today?

[21] **Q:** Today.

[22] **A:** Of course. Because with the data we have [23] today with the patent and the trial, that has [24] been done. Of course we do have it.

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[1] **Q:** And is if somebody had done that in 1997, [2] in fact, it would have been safe and effective?

[3] **A:** No.

[4] **Q:** It would not?

[5] **A:** It would be most probably effective, but [6] we didn't know at all whether it was going to be [7] safe.

[8] **Q:** Regardless of whether you knew it was [9] going to be safe, in fact, it would have been [10] safe. That's what would have happened, right?

[11] **A:** Why? I'm sorry, I can't follow your line [12] of thinking.

[13] **Q:** Okay.

[14] The patient who takes oral [15] alendronate today hasn't looked at clinical [16] trials and doesn't have a lot of knowledge about [17] whether something is safe and effective?

[18] **A:** Correct.

[19] **Q:** So doesn't have all the data that you [20] have. Nevertheless, when the patient takes that [21] oral alendronate once a week at 70 milligrams, [22] that's a safe and effective therapy?

[23] **A:** But the patient doesn't take the drug [24] from the store, the drug store comes to the

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[1] doctor and the doctor explains everything about [2] the drug, everything that has been shown in the [3] trials, then the patient goes away knowing [4] exactly what to expect from these treatments.

[5] **Q:** The patient's state of knowledge doesn't [6] have anything to do with whether or not in fact [7] the dosage is going to be safe or not safe; [8] correct?

[9] **A:** No, I don't agree with you. Because the [10] patient's knowledge comes from the doctor, and if [11] the doctor says that this is going to be safe, [12] then the patient takes that into account.

[13] If the doctor says this is not going [14] to be safe, then the patient is going to follow [15] the suggestion of the doctor.

[16] So the patient cannot formulate an [17] idea and is not also ignorant of what's [18] happening. The doctor is the person —

[19] **Q:** Let me try it again. Let me go back to [20] the original — all I'm asking you, pretty simple [21] question, if somebody had administered oral [22] alendronate once a week in an 80 milligram dose [23] in 1997, had just taken a wild guess, not knowing [24] anything, in fact, that would have turned out to

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[1] be a safe and effective therapy. W know today [2] that's a self and effective therapy.

[3] **A:** That is correct.

[4] **Q:** And if somebody had done that back then, [5] it would have been a safe and effective therapy, [6] regardless of their mental state of whether it [7] would have in fact been safe and effective; [8] correct?

[9] **A:** You mean if a doctor — let me understand [10] your question. If a doctor somewhere out in the [11] bush has given that with absolutely no rationale [12] and without consulting and so on, would it have [13] been effective?

[14] **Q:** Yes.

[15] **A:** Yes.

[16] **Q:** And going back to the — well, let's [17] stick with this one for a few minutes. You say [18] there's no rationale for the dose there. But in [19] fact, at the time that this was published, there [20] was on the market in the United States a 40 [21] milligram dose; is that right?

[22] **A:** Correct.

[23] **Q:** And is it your understanding, is it fair [24] to assume that the author of this article was

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[1] dosing 80 milligrams simply as a multiple of the [2] available dose?

[3] **A:** That's not my interpretation. My [4] interpretation is that this is available, let's [5] try and give this.

[6] **Q:** But it's available, 80 milligrams is [7] available, because the 40 milligrams was [8] available?

[9] **A:** That's right.

[10] **Q:** And that's why he's suggesting 40 [11] milligrams, because he has that available?

[12] **A:** He says take one or two tablets, take [13] them one week per month, one week every three [14] months, et cetera.

[15] **Q:** He has a specific direction about once a [16] week, though, doesn't he?

[17] **A:** Among others, yes.

[18] **Q:** But with the once a week, he gives you [19] the proposed dose for it; right?

[20] **A:** Yes.

[21] **Q:** And he says intravenous administration is [22] possible. And that's true for alendronate; is [23] that right?

[24] **A:** Administration intravenously with

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[1] alendronate?

[2] **Q:** Yes.

[3] **A:** It has been shown before it is possible.

[4] **Q:** He says ibandronate, and says that can be [5] given as an injection every three months rather [6] than as an infusion. Do you see that?

[7] **A:** Absolutely. The fundamental problem here [8] is the following —

[9] **Q:** Let me ask you the question so we'll get [10] through this a little quicker, Doctor.

[11] **A:** Yes.

[12] **Q:** And you say that Boehringer Ingelheim ran [13] a trial with intermittent, with this kind of [14] cyclical therapy, and it didn't work, didn't show [15] a proper efficacy?

[16] **A:** Yes.

[17] **Q:** Boehringer Ingelheim wouldn't have ran [18] the trial unless they had a reasonable [19] expectation that it was going to work. They [20] wouldn't have run it, they wouldn't have invested [21] the money unless they thought it was going to [22] work?

[23] **A:** They had an expectation, yes.

[24] **Q:** They had an expectation, it just turned

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[1] out they made a mistake?

[2] **A:** Yes.

[3] **Q:** And that's a big sophisticated [4] organization?

[5] **A:** Correct.

[6] **Q:** And they made a mistake?

[7] **A:** Yes.

[8] **Q:** So when Dr. Mazess makes this suggestion, [9] he's in pretty good company, isn't he? He's in [10] the company of a company that's sophisticated [11] about this these things?

[12] **A:** He's not a in a company. It's his not [13] his idea, he knows what's going on.

[14] **Q:** He is proposing this because he's [15] reporting news that there's a trial under way?

[16] **A:** Yes.

[17] **Q:** And he's trying to keep you a little more [18] informed; correct?

[19] **A:** Yes correct.

[20] **Q:** That's a reasonable thing to do, there's [21] a trial being carried out by a sophisticated [22] company, and he's reporting on that so people can [23] see what's happening; correct?

[24] **A:** That's what he says. Intravenous

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[1] administration is possible. As you rightly [2] pointed out. Here we have a drug which is the [3] only drug which has shown up until now with good [4] anti-fracture efficacy, and we are trying now, [5] throwing around some suggestions to go someplace [6] else. That's why I'm saying I can't follow this [7] conversation.

[8] **Q:** The ibandronate situation, you seem to [9] think you were critical of him for proposing [10] that. But that was a trial that was going on at [11] the time by a very sophisticated pharmaceutical [12] company; correct?

[13] **A:** Absolutely correct.

[14] **Q:** And in fact, ibandronate, there's a, [15] they're trying that over again, aren't they?

[16] **A:** Not in this way. They did it [17] differently.

[18] **Q:** How did they do it?

[19] **A:** With oral.

[20] **Q:** Aren't they doing a trial even as we [21] speak on injection?

[22] **A:** They increased the dose, and they are [23] doing it under manufacture trial, shorter [24] intervals and higher doses.

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[1] **Q:** It's going on right now?

[2] **A:** It's going on right now.

[3] **Q:** They did an oral trial, a trial of oral [4] dosing of ibandronate with a cyclical regimen?

[5] **A:** Yes.

[6] **Q:** And that shows anti-fracture?

[7] **A:** That's the first time any trial had [8] showed that, and that was reported last year.

[9] **Q:** So Dr. Mazess was right in the sense that [10] he was correct in suggesting that cyclical or —[11] cyclical use of ibandronate can show [12] anti-fracture activity?

[13] **A:** Dr. Mazess from all the suggestion he's [14] making here, he's only at the end of the day [15] correct on only one regimen but with the wrong [16] dose.

[17] **Q:** The wrong dose being 80 milligrams?

[18] **A:** Yes.

[19] **Q:** You think that's the wrong dose?

[20] **A:** He doesn't suggest 70, does he?

[21] **Q:** But we would agree — would you agree [22] with me that 80 milligrams dose would be [23] effective to treat osteoporosis once a week?

[24] **A:** I told you, yes.

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[1] **Q:** So you say he's got a wrong dose?

[2] **A:** Yes.

[3] **Q:** But he's given you a safe and effective [4] dose?

[5] **A:** Why I'm saying that —

[6] **Q:** Could you answer my question, please?

[7] **A:** Yes.

[8] **Q:** I'm sorry.

[9] **A:** The "yes" is not referring to the [10] question. Can you repeat, please, your question.

[11] **Q:** He's suggesting a safe and effective [12] dose, 80 milligrams a week?

[13] **A:** And I said an effective dose, yes.

[14] **Q:** And you don't say a safe dose, because [15] you haven't seen 80 milligrams data?

[16] **A:** I haven't seen any data.

[17] **Q:** You've seen 70 milligrams?

[18] **A:** Today. At that time — today, yes.

[19] **Q:** Based on your state of knowledge today, [20] would you expect that —

[21] **A:** Most likely would be —

[22] **Q:** Safe and effective?

[23] Let me just ask the question so the [24] record is clear.

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[1] **A:** Yes.

[2] **Q:** The dose, Doctor, the dose of 80 [3] milligrams once a week based on today's knowledge [4] you know that would probably be safe and affect I [5] have?

[6] **A:** Most probably, yes, but needs to be [7] tested, of course.

[8] **Q:** And needs to be tested, but nevertheless [9] you would have a reasonable expectation it would [10] be safe —

[11] **A:** My expectation is more or less it's going [12] to be safe and effective, but it needs to be [13] tested.

[14] **Q:** Let's go back to the April '96 Lunar [15] News, which I believe to be a newer version. I [16] think it's Plaintiff's Exhibit 28, page 31. And [17] if we could go to the middle column. The [18] paragraph beginning "one" at the top of the page.

[19] Now, he talks about one of the [20] difficulties with oral alendronate is its low [21] bioavailability. When taken with water in a [22] fasting state, only about 0.8 percent of the oral [23] dose is bioavailable.

[24] And that's a true statement;

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[1] correct?

[2] **A:** Correct.

[3] **Q:** He says even coffee and juice reduces [4] this by 60 percent, and a meal reduces this by [5] greater than 85 percent.

[6] And that's pretty much a true [7] statement; correct?

[8] **A:** Correct.

[9] **Q:** He says that alendronate must be taken [10] after an overnight fast 30 to 60

minutes before [11] breakfast, and that was in accordance with [12] Merck's existing instructions at the time; [13] correct?

[14] **A:** Correct.

[15] **Q:** And subjects should remain seated or [16] standing. And he then says a small group of [17] patients have reported some upper GI distress if [18] this is not done. And that's correct, isn't it?

[19] **A:** I would not agree with the very small [20] group.

[21] **Q:** You would consider it larger than a very [22] small group?

[23] **A:** Yes.

[24] **Q:** But other than quarreling with the size

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[1] of the group, would you agree?

[2] **A:** If this is not done, that's part of the [3] issue, because what he's referring here, GI side [4] effects in relation to taking the drug [5] incorrectly.

[6] So some of that refers to that. But [7] he misses the rest.

[8] **Q:** As far as it goes, though, it's correct?

[9] **A:** Yes.

[10] **Q:** This regime may be difficult for the [11] elderly to maintain chronically, and that's a [12] true statement; correct?

[13] **A:** Yes.

[14] **Q:** Then he says an intermittent treatment [15] program, for example, once per week or one week [16] every three months, with higher oral dosing needs [17] to be tested. Do you see that?

[18] **A:** Yes. I saw that.

[19] **Q:** So he's proposing using alendronate once [20] per week; correct with higher oral doses?

[21] **A:** He's proposing an intermittent drug.

[22] **Q:** And part of that intermittent — one [23] option of the intermittent, one option of that [24] program is once per week?

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[1] **A:** Which is fundamentally different.

[2] **Q:** From what?

[3] **A:** Because once per week is not an [4] intermittent regimen.

[5] **Q:** You don't use the words — you don't say [6] intermittent to describe once per week?

[7] **A:** No.

[8] **Q:** You don't think anybody in his right mind [9] would use intermittent to describe —

[10] **A:** I don't think that anybody has used the [11] word intermittent to describe it, to my [12] knowledge, at least from the people knowledgeable [13] in the field.

[14] **Q:** And the use of intermittent to describe [15] once a week, that would demonstrate to you [16] ignorance of this field; is that right?

[17] **A:** It demonstrates to me that you cannot [18] dissociate between the two. So for him, in his [19] mind, once a week, and one week every three [20] months means exactly the same thing, which are [21] fundamentally different.

[22] **Q:** And nevertheless, it's clear to you when [23] he says once per week, what he means by once per [24] week? There's no ambiguity about that phrase?

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[1] **A:** Oh, no. That's clear.

[2] **Q:** And he's recognized that if you're going [3] to do it once per week, you have to use a higher [4] oral dose; correct?

[5] **A:** Yes.

[6] **Q:** And —

[7] **A:** Yeah.

[8] **Q:** Someone skilled in the art at this time [9] would have recognized that that higher oral dose [10] should be about 70 milligrams; correct, for the [11] treatment of osteoporosis?

[12] **A:** The real skilled in the art, yes.

[13] **Q:** And by July 1977, that is, sometime after [14] this publication, a 5-milligram dose had been [15] approved for prevention of osteoporosis; correct?

[16] **A:** I'm not familiar with exact date of [17] approval. But if you say that, I take your word [18] for it.

[19] **Q:** Okay. '97.

[20] I misspoke. July '97. [21] Does that help you? So by July '97.

[22] **A:** It was approved in July '97.

[23] **Q:** I think it was approved — I'll represent [24] that it was approved before July '97, but I'm

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[1] not —

[2] **A:** So, yeah. I take your word if you say [3] that. I don't — I don't know.

[4] **Q:** Okay. I assume that I'm correct, and the [5] record —

[6] **A:** Yeah.

[7] **Q:** — will belie that if I'm not.

[8] **A:** Mm-hmm.

[9] **Q:** Someone who was aware of that would [10] understand that the weekly dose should then be 35 [11] milligrams to correspond?

[12] **A:** Where am I?

[13] **Q:** The higher oral —

[14] **A:** Are we looking on the same —

[15] **Q:** The higher oral. If you're going to do [16] it once a week, the higher oral dose, that's [17] referring to what should be 35 milligrams a week?

[18] **A:** Why?

[19] **Q:** If it is — if you understood that the [20] five milligrams a week was available for [21] prevention on a daily basis.

[22] **A:** It doesn't.

[23] **Q:** I mean, 5 milligrams a day.

[24] **A:** He doesn't make any suggestion that the

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[1] dose in once a week should be seven times the [2] daily dose.

[3] Where do you see that? I'm sorry.

[4] **Q:** Well, you told me just two minutes ago, [5] Doctor, that someone skilled in the art looking [6] at that would recognize that the higher oral dose [7] for treatment should be 70 milligrams a week.

[8] **A:** It would be 70, because we know that we [9] can do it like that, yes.

[10] **Q:** And because, and again, somebody looking [11] at that would understood that the higher oral [12] dose he's referring to for prevention should be [13] 35?

[14] **A:** I see what you mean. Yeah. That would [15] probably be about —

[16] **Q:** Okay. Let me show you an exhibit that we [17] used this morning. It's Defendant's 192.

[18] **A:** Do I have it here?

[19] **Q:** No. I'm going to put it up on —

[20] **THE WITNESS:** I have to find a [21] copy.

[22] **MR. GALBRAITH:** Let me just dig it [23] out. I apologize, Your Honor.

[24] **BY MR. GALBRAITH:**

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[1] **Q:** Were you in the courtroom this morning [2] when Dr. Yates talked about this document?

[3] **A:** Which document?

[4] **Q:** The one that's on the board, Defendant's [5] Exhibit 192. I'll give you a copy of it.

[6] **A:** Yes. I was there at that meeting, but I [7] can't say that I can recall the details of that [8] meeting.

[9] **Q:** Okay. Well, if we could turn to the — [10] it's the letter — I think it's the second page [11] of the exhibit or third page of the exhibit. If [12] you could blow up the second paragraph, Stan.

[13] **A:** What page should I look at?

[14] **Q:** I'm sorry. It's the third page of the [15] document, third page in from the top.

[16] You see the background. This is a [17] background document submitted to the FDA from [18] Merck?

[19] **A:** Yes. Yes.

[20] **Q:** And this paragraph says, "This background [21] document summarizes the proposed MRL clinic". Do [22] you understand that to be Merck Research [23] Laboratories?

[24] **A:** Yes.

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[1] **Q:** Clinical development program with [2] alendronate at oral doses of 35 and 70 [3] milligrams, administered once weekly or twice [4] weekly in the treatment and prevention of [5] postmenopausal osteoporosis.

[6] And do you see down what — how they [7] refer to this in the second line from the bottom, [8] these intermittent dosing regimes?

[9] **A:** Where are you?

[10] **Q:** As described in the —

[11] **A:** Where should I look? Further down in the [12] same?

[13] **Q:** If you look —

[14] **A:** Yeah. Yes.

[15] **Q:** So —

[16] **A:** I see what they're writing.

[17] **Q:** So Merck describes —

[18] **A:** Yes.

[19] **Q:** — these once-a-week dosing regimens as [20] intermittent; is that correct?

[21] **A:** That is what they say here, yes.

[22] **Q:** And so you think Merck is using improper [23] terminology there?

[24] **A:** I'm not responsible for this for the

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[1] statements made by Merck. I said what was [2] scientifically sound at that time.

[3] **Q:** So you think that was scientifically [4] unsound?

[5] **A:** In that opinion, yes, despite the fact [6] that I'm here with — I mean, testifying on [7] behalf of Merck.

[8] **Q:** So if Dr. Mazess was scientifically [9] unsound to call that, his program intermittent, [10] call once a week intermittent, at least he's in [11] good company here; isn't that right?

[12] **A:** Absolutely. Absolutely.

[13] **Q:** Now, as I understand your testimony, you [14] were — you did receive the Lunar News. And [15] although I think you testified in your deposition [16] maybe, or maybe here that you didn't read the [17] articles regularly, but that you did find the [18] bibliographies quite useful at the time?

[19] **A:** Yes.

[20] **Q:** That's the principal use you made of the [21] Lunar News and to go through and use it to help [22] you as a source of primary sources, if you will?

[23] **A:** Yeah. It was before the internet era, so [24] it was a very useful source of references.

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[1] **Q:** Now, you testified some about all these [2] other dronates, if I can call them that, that [3] preceded alendronate. And is it fair to say that [4] as of July 1997, there was a lot more clinical [5] and real-world information available to those [6] skilled in the art about alendronate than there [7] was about any of these other predecessor [8] bisphosphonates?

[9] **A:** In terms of numbers of patients studied; [10] yes.

[11] **Q:** And I think you talked a little bit about [12] Paget's statements — Paget's patients. And is [13] it true that Paget's patients are often [14] discovered fortuitously during routine or during [15] other physical exams?

[16] **A:** Correct. Usually when you take blood for [17] other reasons, and you find a raised blood level.

[18] **Q:** And so a lot of these patients, a lot of [19] these people for whom this condition is [20] discovered, when it's discovered, they're not [21] coming in there for the pain of Paget's disease. [22] They're coming in there for some other reason, [23] and the doctor fortuitously discovers that or [24] notices that they have a biochemical marker —

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[1] marker that he associates with Paget's disease; [2] is that right?

[3] **A:** In old clinical series, at least [4] published by the Men's Centers, these kind of [5] patient accounts for less than 10 percent of the [6] population treated.

[7] **Q:** But you would agree that often such [8] patients are treated, notwithstanding that they [9] don't have symptoms?

[10] **A:** I wouldn't use the word often. Today, [11] yes.

[12] As I explained earlier, today our [13] thoughts are different in the management of [14] Paget's disease. But at the time of question, [15] this was not the case.

[16] And you can see that from the clinic [17] series.

[18] **Q:** So you're saying today you would treat [19] these asymptomatic patients whereas a few years [20] ago the time in question here, in 1997, you would [21] not do so; is that right?

[22] **A:** I'm saying that today more and more of [23] these people are being treated. At that time, it [24] was in the clinical practice, the smaller and

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[1] very, very small group of patients, as I said, [2] less than 10 percent.

[3] But people interested in Paget's [4] disease and trying to follow the natural course [5] of the disease where we were trying to get these [6] kind of patients to see whether what we're saying [7] today could be proved.

[8] **Q:** Well, as of 1997, do you think that it [9] was believed in the field that treatment should [10] be offered to asymptomatic patients with [11] involvement of skeletal areas that have a [12] potential to give rise to complications, that is, [13] is that the conventional standard?

[14] **A:** The answer is no. Certainly, the United [15] States, because the only available treatments for [16] treatment of Paget's disease at that time was [17] etidronate oral, which induces osteomalacia, and [18] you don't want to put an asymptomatic patient [19] with that, without symptoms, to put these [20] patients into this kind of treatment.

[21] And secondly, the other available [22] treatment, which became in the United States [23] available in the early 1990s was intravenous [24] pamidronate, which means that you're going to

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[1] take a patient without symptoms and admit to the [2] hospital, give infusions of pamidronate.

[3] So I believe that, at that time with [4] what we had available, treatment to patients with [5] no symptoms was not offered.

[6] **Q:** Let me put up on the screen an excerpt [7] from Dr. Fleisch — Fleisch's book, [8] Bisphosphonates In Bone Disease. And it's the [9] 1995 edition, and it's Defendant's 531.

[10] And if you —

[11] **A:** Can I have a copy as well, please?

[12] **Q:** Oh, yeah. I have an extra one.

[13] It's a little hard to see the [14] screen, isn't it?

[15] **A:** Thank you.

[16] **Q:** And you recognize this as the — as [17] the — Dr. Fleisch's book about which you [18] testified?

[19] **A:** Yes.

[20] **Q:** Or an excerpt. Could you turn to Page [21] 72?

[22] **A:** Hold on. Let me —

[23] **Q:** And under treatment with drugs other than [24] bisphosphonates, it says, " Treatment should be

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offered to all symptomatic patients, as well as to asymptomatic patients wit involvement of skeletal areas that have a potential to give rise to complications, such as the skull, vertebral" — "vertebral bodies, long bones, and near major joints."

Is that in accordance with the standard of care in 1995?

A: No. Because as I told — I explained to you why, unless this was a time where alendronate had already been approved.

Had it been approved by then?

Q: I don't know. I don't know when this book came out, other than the year.

A: Because at that stage in the United States, the only available treatment were etidronate, and intravenous etidronate. I don't think that any responsible physician was going to treat asymptomatic patients with that.

But if you had, as we had in Europe, oral clodronate, which was very — it was quite potent for the disease, and it was very well tolerated, then yes, a British doctor or a Dutch doctor might treat such patient with the

availability with clodronate.

Q: Okay. In 1997, by July of 1997, you understand that the 40 milligram was approved in the United States?

A: And that is one way of thinking. It started slow, slow change, and with the introduction later of residronate, which can be given for two months.

Q: So you don't —

A: Only.

Q: — agree?

A: So we started looking more and more into this kind of population.

Q: So you don't agree that in the — in errancy of the Bible here; is that right?

A: No, it's not that I don't agree. I'm saying if I were in Europe, and I was reading, and if I had clodronate available, I could do it.

But if it were in the United States, yes, I wouldn't follow the suggestion of Professor Fleisch. And I don't think that physicians in the United States were following at that time this kind of approach.

Q: And, Doctor, you've testified a little

bit about the Ettinger article, I think, at Plaintiff's 124 in the book.

A: What did you say? I'm sorry.

Q: The Ettinger.

A: Yes. Yes. What time?

Q: 124.

A: Yes.

Q: And I thought — I thought I heard you refer to that as a clinical study; is that right?

A: I said it was a report rather than a study.

Q: It was a report. Okay.

A: And I made a very clear comment, I think, regarding the scientific value of that particular article.

Q: And the scientific value is essentially zero; correct?

A: Not zero, no. But, I mean, because the people have done surveys, so on and so on, so it's not zero. But it's not scientifically very interesting.

On the other hand, it's clinically extremely important.

Q: Do you know what position Merck took when

this article came out?

A: No.

Q: Are you aware that Merck issued press releases and tried to stop the publication of this article?

A: I'm not aware of that. That's the first time I've heard about it.

Q: And that Merck strongly disagreed with this article and the companion article that went with it?

A: I don't know that.

MR. GALBRAITH: Put 534 up.

THE WITNESS: Do I need the paper or?

BY MR. GALBRAITH:

Q: I'm going to show it to you. I put it up on the screen.

I'll give you a copy of Defendant's 534, which is a Merck statement on the publication of the Ettinger surveys.

Have you read this before?

A: No.

Q: Do you see in the second full paragraph it says, We strongly disagree with the conclusion

of both parties?

A: Can I — can I read it —

Q: Sure.

A: — quickly because —

MR. LYNCH: Objection, Your Honor. This is — this is an effort to get an anti-Merck document up with some someone who's never dealt with it before.

MR. GALBRAITH: Your Honor, he testified about the survey. I think I'm entitled to explore his views about Merck's reaction to it.

THE COURT: Mm-hmm. All right. The objection is noted THE WITNESS: Objection? So what do I do now?

I'm reading that; right?

MR. GALBRAITH: Okay.

BY MR. GALBRAITH:

Q: Do you see that Merck strongly disagreed with the conclusions of the articles?

A: In the second paragraph?

Q: Yes.

A: Yes. I see that.

Q: And did you take Merck's views of these articles into account before you gave your opinions?

A: No. And I can understand why Merck disagrees with this document.

Q: Because they don't think — they don't think it's scientifically sound; right?

A: No. No. No.

Merck has the data from the clinical trials, which show no difference between the groups. I mean, it is very well-tolerated alendronate, equally well to placebo, so they have this document.

And here comes a study from daily practice, which does not fit with what they had collected up until then. And I believe because they didn't have any such data themselves, they disagree with that.

But I'm not speaking for Merck now, because I don't know what their position is. But that's how I would do that.

On the other hand, myself, who I can both interpret clinical trials and take part in clinical trials, but at the same time, I have

real-life experience. I can see the point of Dr. Ettinger, because Ettinger's experience, although exaggerated a bit, fit very well. My experience fit very well with big studies that we have done Phase IV in the Pharmaco-Vigilant studies, et cetera.

So it was very clear to me.

Q: You don't agree with Merck that the studies and conclusions reached by Ettinger in these studies are scientifically accurate and potentially harmful to patients?

A: That's a statement of Merck. I'm not responsible for the statement.

Q: I know you're not responsible. I'm not saying it's your statement, but I'm

asking you [16] whether you agree or disagree. It's the [17] statement on the last page, the overall [18] assessment.

[19] **A:** Where do I look?

[20] **Q:** Last page of the exhibit.

[21] **A:** Finally?

[22] **Q:** Well, —

[23] **A:** It starts with finally?

[24] **Q:** Starting with, Finally, as we started

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[1] earlier, we felt that the conclusions reached by [2] Ettinger, et al, in both of these two studies are [3] scientifically inaccurate and potentially harmful [4] to patients.

[5] Do you agree with that statement?

[6] **A:** I agree that what they say scientifically [7] isn't correct, and I told you before that. And [8] the statement that they can be potentially [9] harmful to patients, I disagree with that [10] statement.

[11] **Q:** Now doctor just so I'm clear, you have [12] never prescribed the 40 milligram alendronate [13] dose; is that right?

[14] **A:** Never. It was not available in the [15] Netherlands, and I believe in the whole of [16] Europe.

[17] **Q:** And you would agree with me, would you [18] not, that in terms of predicting whether the [19] 70-milligram dose would be tolerated — would be [20] well tolerated by patients, 70-milligram [21] once-a-week dose would be well tolerated by [22] patients, that the pamidronate data is not as [23] relevant as the clinical data with respect to [24] alendronate used in Paget's patients?

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[1] **A:** I wouldn't agree entirely with you, [2] because the pamidronate has also been used in all [3] types of patient populations. So you have a good [4] profile.

[5] And then you go to see what happened [6] with alendronate. Of course, you can't use the [7] data of pamidronate only to talk about [8] alendronate. This is obvious.

[9] You need to look at the data of [10] alendronate itself.

[11] **Q:** Well, on a scale of relevance, wouldn't [12] you put alendronate in Paget's a bit higher up [13] than pamidronate in osteoporosis?

[14] **A:** I don't honestly know.

[15] **Q:** Could we —

[16] **A:** Most probably, yes, I would say, because [17] it's — it is the relevant drug, although in a [18] different disease. But I would use my thinking, [19] and my extrapolations combined with the data I [20] have in osteoporosis for alendronate.

[21] If I didn't have any data on [22] osteoporosis alendronate, and you would ask me, [23] Dr. Papapoulos, we're going to do something in [24] osteoporosis. We have data with pamidronate and

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[1] in osteoporosis, and we have data with [2] alendronate in Paget's disease.

[3] What are you going to do? [4] Then, there, most probably, I'm [5] going to combine the experience and the weight of [6] the data in Paget's with alendronate. But if I [7] have data in osteoporosis, and this fits in tying [8] with my data with pamidronate in osteoporosis, [9] then I don't have to look anywhere else.

[10] **Q:** Now, in your — in the Netherlands, as I [11] understand it, the withdrawal rate from [12] alendronate in your daily — in the daily dose is [13] in the order of 12 percent; is that correct?

[14] **A:** That is absolutely correct.

[15] **Q:** For GI side effects?

[16] **A:** For GI side effects. And we know that in [17] the study with 11,000 patients where we had about [18] 12-percent withdrawals due to GI side effects [19] within the first six weeks. It is in my [20] deposition.

[21] **Q:** And those are patients taking the [22] 10-milligram dose?

[23] **A:** The 10-milligram, yeah. Mm-hmm.

[24] So my experience,

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[1] Pharmaca-Vigilance, and Ettinger's experience is [2] different from the clinical trials.

[3] **Q:** If we could look at Plaintiff's Exhibit [4] 115 that you testified to in your direct.

[5] **A:** What did you say? I'm sorry.

[6] **Q:** 115.

[7] **A:** I don't think I have 115.

[8] **Q:** 115?

[9] **A:** Sorry.

[10] **Q:** I believe you should have it. It's the [11] Kanis article.

[12] **A:** The paper of Dr. Kanis.

[13] **Q:** And this is — you referred to a passage [14] from this book. Sorry, from this article, and it [15] appears on Page 10 of the article.

[16] **A:** Yes, sir.

[17] **Q:** Is the — and the statement you referred [18] to says most frequently reported side effects is [19] gastric intolerance, which is dose dependent, and [20] occurs in about 10 percent of patients after oral [21] treatment with doses of 40 milligrams daily or [22] more.

[23] Now, is that — do you understand [24] that to be a reference to the — to the Chestnut

Page 703

[1] data?

[2] **A:** It may be, it may not be, because he is [3] not referring specifically to that.

[4] **Q:** He gives no reference at all to what?

[5] **A:** Yeah. It may have been to that.

[6] But the point is, as I said before, [7] here I have an authority writing it.

[8] **Q:** I'm sorry, Doctor. I just have a [9] question for you.

[10] **A:** Oh, I'm sorry. I thought —

[11] **Q:** And that is: Are you aware of — did you [12] hear the testimony that Merck had no other [13] 40-milligram studies —

[14] **A:** Yes.

[15] **Q:** — in osteoporosis?

[16] **A:** Yes.

[17] **Q:** Other than the 10 milligram study, —

[18] **A:** Yes.

[19] **Q:** So you assume this is the Chestnut study?

[20] **A:** Now, that we're discussing that, yeah. [21] When I read the article back in 1995, no.

[22] **Q:** You don't assume —

[23] **A:** And every other person skilled in the art [24] would not read it like that. You could say oh,

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[1] perhaps this is the other study, the Chestnut, or [2] perhaps since he's not reporting anything, [3] perhaps he means something different.

[4] So I'm talking about the time of [5] publication.

[6] **Q:** So every time you saw this reference to [7] 10 percent of patients reporting gastric [8] intolerance at 40 milligrams daily, you assumed [9] it was, each time it's reported, it's a different [10] study?

[11] It didn't occur to you that it might [12] be the same study?

[13] **A:** It might be the same study, but I wasn't [14] sure, because I was surprised because there was [15] no physician involved in this study that didn't [16] refer to their study. So because it was never [17] referred to, I couldn't — I couldn't make any [18] kind of conclusion of that.

[19] **Q:** So because there was no reference, nobody [20] told you what study it was, you could say — you [21] could conclude it's maybe another study?

[22] **A:** Maybe.

[23] **Q:** Maybe it's not?

[24] **A:** Maybe.

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Q: Okay.

A: For me, the most important thing was the conclusion of Dr. Kanis.

Q: And when Dr. Fleisch reports the similar observation, again, that comes from the Chestnut study, doesn't it?

A: That's probably — yes, I mean.

Q: That's not work by —

A: Yes.

Q: Dr. Fleisch doesn't do clinical trials; right?

A: Of course not.

Q: Doctor, I'm putting up on the screen a copy of — and I think it's a chapter written by you, from a book called The Aging Skeleton. And it's Defendant's Exhibit 527.

A: Can I have a copy of it?

Q: I'm getting a copy.

I have a copy.

A: Thank you.

Q: Is this a chapter that you wrote?

A: Yes.

Q: And on the Page 543, which is the fourth, the fifth page of the exhibit —

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A: Which one are you saying?

Q: 543.

A: 543.

Q: In the first full paragraph, it begins with bisphosphonates.

A: Yes.

MR. LYNCH: Objection, Your Honor. I've never received a copy of this exhibit before.

The last one we have is 523. I'm just saying we weren't told.

MR. GALBRAITH: This is cross-examination. I don't know what kind of rule that we have that provides cross-examination exhibits are —

MR. LYNCH: Your Honor, my thought was that if this is an exhibit for impeachment, it's fine. But then if it's not an exhibits, it's used for impeachment. That's what I had understood the rule was. If you want it to be an exhibit, it's an exhibit.

MR. GALBRAITH: Your Honor, the exhibit I used for impeachment, or tried to impeach with Dr. Russell, they put the numbers on

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later and sent them to us.

I'm just putting them on in advance.

MR. LYNCH: That's what this is?

BY MR. GALBRAITH:

Q: Well, any way. Sorry, Dr. Papapoulos.

A: Please carry on.

Q: Do you see the chapter, the paragraph beginning Bisphosphonates?

A: Oh, yes, I do.

Q: And he says in referring to bisphosphonates, you say rather, in the second sentence differences. Do you see that?

A: Yes.

Q: Differences also exist in their pharmacological and toxicological profiles as well as in their mechanism of action. It is, therefore, important that the specific properties of every individual bisphosphonate be determined and that result obtained with one bisphosphonate, not be extrapolated readily to the whole class.

And that's a statement that you endorsed today; is that correct?

A: This is an excellent statement to which I referred also earlier of during in this

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afternoon.

MR. GALBRAITH: I have no further questions, Your Honor. Thank you.

BY MR. LYNCH:

Q: One thing I want to go back to. You have this little discussion with Mr. Galbraith about treating Paget's patients.

Go to 531. You had some discussion, about two sentences.

A: 531, you say?

Q: Yes. That's the — the chapter from —

A: From Fleisch.

Q: Dr. Fleisch; right?

A: Yes. 70.

You said 73.

Q: 72?

A: 72. Yes.

Q: Now, you concentrated — could you get that up there?

No. This is — this is 531.

(Following a discussion held off the record:)

BY MR. LYNCH:

Q: We'll put up — we don't have this one,

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either?

A: I mean, —

MR. LYNCH: We didn't get this one, either.

THE WITNESS: I have it here.

MR. LYNCH: I was asleep at the switch.

THE WITNESS: I have it here. I read it.

BY MR. LYNCH:

Q: You have it. You have it. Okay. Now, —

MR. GALBRAITH: Do you want us to put it up Mr. Lynch?

MR. LYNCH: Yeah, put it up.

THE WITNESS: It's at Page 572?

BY MR. LYNCH:

Q: 531, Page 572.

All right. Now, good. You focused on — counsel was suggesting to you that Paget's patients should be treated if they're asymptomatic. Let's take a look at everything that Dr. Fleisch said.

A: I saw that he says, Dr. Fleisch, however,

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many patients, especially those of whom diagnosed were fortuitous, and who have no symptoms need no treatment. So at the end of the day, I was not so much in difference with his opinions.

Q: Now, one thing. In connection, you testified about the tolerability that Paget's patients and osteoporosis patients have shown to a number of bisphosphonates; is that correct?

A: For a number, no. I said I have the experience from pamidronate.

Q: You have the experience, and the literature reflects that there is such a situation for alendronate as well?

A: Yes.

Q: Is that correct?

A: Yes.

Q: Now, and you indicated that that was something you could not explain?

A: Yes.

Q: My question is: Do you have an opinion as to whether the fact that there is a difference in the toleration level between those two kinds of patients is something that's widely recognized or recognized by those skilled in this metabolic

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bone disease or not?

MR. GALBRAITH: Objection. Beyond the scope of cross.

THE WITNESS: Sorry?

THE COURT: Objection is noted. Beyond the scope.

You can answer.

THE WITNESS: Can I carry on?

[9] **THE COURT:** Yes, you may.

[10] **THE WITNESS:** Certainly for people [11] who have experience in using these drugs both in [12] package and in osteoporosis.

[13] **BY MR. LYNCH:**

[14] **Q:** I'm sorry. Do you have an opinion that [15] they would have such an understanding?

[16] **A:** That physicians who use bisphosphonates [17] in treating both Paget's and also osteoporosis [18] would probably have this understanding.

[19] **MR. LYNCH:** No further questions, [20] Your Honor.

[21] **THE COURT:** All right. Thank you [22] Doctor.

[23] **THE WITNESS:** Thank you.

[24] **MR. BARZOUKAS:** Your Honor, Merck

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[1] calls Dr. Christopher Vellturo.

[2] **MR. GALBRAITH:** Your Honor, would [3] this be an okay place to take a break for us to [4] reorganize?

[5] **THE COURT:** I was going to take a [6] break at 3:00 to deal with a conference. But we [7] can break now.

[8] **MR. GALBRAITH:** That's fine. We can [9] break at 3:00.

[10] **THE CLERK:** Please state and spell [11] your full name for the record, please. [12] Christopher Vellturo, V-E-L-L-T-U-R-O.

[14] CHRISTOPHER VELLTURO, [15] the witness herein, having first been [16] duly sworn on oath, was examined and [17] testified as follows:

[19] **DIRECT EXAMINATION**

[20] **BY MR. BARZOUKAS:**

[21] **Q:** Good afternoon, Dr. Vellturo.

[22] **A:** Good afternoon.

[23] **Q:** Dr. Vellturo, could you just briefly [24] summarize for us your educational experience?

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[1] **A:** Yes. I have a bachelor of science degree [2] in applied mathematics and economics from Brown [3] University in Province, Rhode Island, and a Ph.D. [4] in economics from MIT in Cambridge, [5] Massachusetts.

[6] **Q:** Did you concentrate your study in any [7] particular areas?

[8] **A:** Yes, I did. At MIT, you have to choose [9] two fields that are going to be your field of [10] specialty, and I chose and pursued industrial [11] organization and econometrics.

[12] **Q:** And could you explain for us those [13] disciplines briefly?

[14] **A:** Sure. Industrial organization is a [15] subdiscipline of something called microeconomics. [16] And what industrial organization does is it [17] studies how markets form and how firms interact [18] and compete in those markets and how — not only [19] between each other, but how they interact and [20] compete for customers, as well. So that's [21] industrial organization.

[22] Econometrics is the application of [23] statistical and possibilistic theory and [24] applications to economic data.

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[1] **Q:** And Dr. Vellturo, what have you done [2] since you finished with your studies?

[3] **A:** Since that time, I've taken those two [4] specialty fields, industrial organization and [5] econometrics, and I have applied them to a wide [6] variety of specific market problems in the [7] context of many different markets in many [8] different kinds of issues.

[9] **Q:** Have you concentrated professionally in [10] any particular areas?

[11] **A:** No. I'd say that my work has been pretty [12] broad based. I've done a lot of merger work [13] that's taken me before various regulatory [14] agencies in the United States and around the [15] world. I've done some work for commercial [16] success issues in patent cases such as this. [17] I've done work on damages issues in patent cases. [18] It's been a very broad array.

[19] **MR. BARZOUKAS:** Your Honor, Merck [20] offers Dr. Vellturo as an expert in economics.

[21] **MR. GALBRAITH:** No objection.

[22] **BY MR. BARZOUKAS:**

[23] **Q:** Dr. Vellturo, did you receive an [24] assignment with respect to this case?

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[1] **A:** I did.

[2] **Q:** And could you describe the assignment?

[3] **A:** I think the assignment I received was to [4] evaluate whether Fosamax once weekly had been [5] commercially successful in the marketplace, and [6] whether that success could be attributed to the [7] characteristics of the product associated with [8] the Daifotis patents.

[9] **Q:** And did you reach any conclusions after [10] your analysis?

[11] **A:** Yes, I did.

[12] **Q:** And what were those conclusions?

[13] **A:** There were two. The first would be that [14] once weekly was indeed a commercially successful [15] product, and that its commercial success could be [16] at least in part, significant part, attributable [17] to the Daifotis patents.

[18] **Q:** Now, did you perform any background work [19] in order to do your analysis?

[20] **A:** I did.

[21] **Q:** And what did you do?

[22] **A:** Let's see. I certainly read the patents. [23] That was an interesting exercise. I looked at [24] business documents of the parties in this case

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[1] that were produced. I collected some publicly- [2] available information, as well. I went and met [3] with Merck individuals who are involved in both [4] the osteoporosis side of their business and also [5] their market research people. I collected data [6] from a number of sources, including IMS, a very [7] extensive and common source for information on [8] prescriptions of pharmaceuticals. And I put that [9] all together, and I've conducted an analysis of [10] commercial success, and I was asked to write a [11] report about my findings, and I did so. And I [12] was, I think, deposed sometime in January, and [13] here I sit.

[14] **Q:** You mentioned IMS. Could you explain a [15] little bit more what IMS is?

[16] **A:** IMS is a — they used to be a subsidiary [17] of Dunn & Bradstreet, but I think they've spun [18] off on their own now; they're independently [19] incorporated.

[20] They're a data collection firm, and [21] they specialize in the medical industry, but they [22] particularly specialize in collecting data on [23] prescribing patterns of physicians but also [24] prescriptions volumes as they flow through drug

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[1] stores and other avenues.

[2] **Q:** Do you have any knowledge particularly [3] about the underlying data that they collect?

[4] **A:** Yeah, I do. I actually worked on a [5] merger for IMS, actually a series of mergers for [6] IMS over the last five to seven years. I've [7] spent a great deal of time with their business [8] people and their data people.

[9] And so aside from the fact that I [10] use it all the time when I study pharmaceutical [11] industries, I've actually worked with them and [12] specifically spent time with them understanding [13] how they collect their information.

[14] **MR. BARZOUKAS:** Your Honor, you [15] mentioned you were going to take a break at 3:00, [16] and this may be a good point to do so.

EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK & CO., INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No. 01-048 (JJF)
	)	
TEVA PHARMACEUTICALS USA, INC., and	)	
	)	
Defendant.	)	
	)	

TEVA PHARMACEUTICALS USA'S
RESPONSE TO MERCK'S FIRST SET OF DOCUMENT REQUESTS (1-60)

Pursuant to Rule 34 of the Federal Rules of Civil Procedure, Teva responds to Merck's First Set of Document Requests as follows.

Each response is subject to all objections as to competence, relevance, materiality, propriety and admissibility, and to any and all other objections on any grounds that would require the exclusion of any statements contained herein if such responses were asked of, or statements contained herein were made by, a witness present and testifying in court, all of which objections and grounds are expressly reserved and may be interposed at the time of the trial.

The following responses are based upon information and writings currently available and located by Teva and the responses given herein are without prejudice to Teva's right to supplement or to revise these responses if further investigation or discovery so indicates.

Teva's responses shall not be deemed to constitute admission (i) that any particular document or thing exists, is relevant, non-privileged, or admissible in evidence, or (ii) that any statement or characterization in Merck's Document Requests is accurate or complete. In

addition, willingness to produce documents in response to any particular request is in no way a concession that such documents exist, or that any such documents are within Teva's possession, custody or control.

GENERAL OBJECTIONS

Teva's specific responses to all Merck's document requests are subject to the following General Objections, which are incorporated by reference in each response.

General Objection 1

Teva objects to each document request that is inconsistent with or seeks to impose an obligation beyond that required by the Federal Rules of Civil Procedure taken together with the Local Rules of the District of Delaware.

General Objection 2

Teva objects to the production of any documents or things which are subject to the attorney-client or joint defense privilege or work product immunity. In due course, following a completion of production of documents, Teva will provide a log of documents withheld from discovery on the grounds of attorney-client privilege, work product immunity, or both ("Privileged Document Log"), in exchange for such a log from Merck. Any inadvertent disclosure of such information shall not be deemed a waiver of the attorney-client privilege, the work-product doctrine, or any other applicable privilege or immunity.

General Objection 3

Teva objects to the identification or production of any documents or things dated or prepared after the filing date of the Complaint in this action as being overly broad and unduly burdensome.

General Objection 4

Teva objects to each document request that is vague, indefinite, overly broad, unduly burdensome, and/or oppressive because the burden on Teva to search for, gather and produce such documents, if any, far outweighs the relevancy of such documents, nor are such documents likely to lead to the discovery of admissible evidence.

General Objection 5

Teva objects to each request to the extent it seeks production of "all documents" responsive to the requested categories on the grounds that such request is overly broad, unduly burdensome, oppressive, and not reasonably calculated to lead to the discovery of admissible evidence. Subject to these objections, Teva will use reasonable diligence to locate documents in its own files, based on an examination of those files reasonably expected to yield responsive documents, or summary information to the extent it is available. As used in these responses, the phrase "all documents," or phrases of similar import, should be understood to mean those documents Teva and its counsel were able to locate using reasonable diligence and judgment concerning the whereabouts of responsive documents, or a summary of those documents.

General Objection 6

Teva objects to each document request to the extent it seeks the identification or production of documents or things that are in the public domain and therefore of no greater burden for Merck to obtain than for Teva.

General Objection 7

Teva objects to each document request to the extent it seeks the identification or production of any and all documents and things that are otherwise producible but which contain confidential or proprietary information, except as provided by the District of Delaware local rules

or pursuant to a Protective Order entered in this case.

General Objection 8

Teva objects to the production of the following categories of documents on the grounds that the requests seeking these categories are overly broad, unduly burdensome, and not relevant to the subject matter of this litigation nor reasonably calculated to lead to the discovery of admissible evidence: (I) documents filed in this action and copies of communications between attorneys in this litigation; (ii) documents relating to settlement negotiations; (iii) duplicative or cumulative documents; and (iv) documents already in the possession of Merck.

General Objection 9

Teva objects to each document request to the extent it seeks the identification or production of third party documents that are covered by a third-party confidentiality agreement.

General Objection 10

Teva reserves the right to mask or delete materials from any document or thing that it produces to the extent that such materials are not responsive to any of Merck's requests, not relevant to the subject matter of this action, or not reasonably calculated to lead to the discovery of admissible evidence. Teva also reserves the right to mask or delete materials that are protected from disclosure by the attorney-client privilege, attorney work-product doctrine and/or otherwise immune from discovery.

General Objection 11

Teva objects to each document request to the extent it seeks the identification or production of any document relating to any FDA filing other than ANDA No. 75-710. Teva further objects to each document request to the extent it seeks identification or production of documents relating to ANDA No. 75-710 that are not relevant to this action.

General Objection 12

Teva objects to each document request to the extent it seeks the identification or production of documents relating to any biphosphonate other than the weekly dose forms of alendronate that are the subject of Teva's October 23, 2000 and August 20, 2001 amendments to ANDA No. 75-710 .

General Objection 13

Teva objects to each document request to the extent it seeks information relating to Teva's activities outside the United States, including legal proceedings or any efforts to seek marketing approval in a country other than the United States.

General Objection 14

Teva objects to each document request to the extent it seeks information relating to U.S. Patent Nos. 5,358,941, 5,681,590, 5,849,726, 6,008,207 and 6,090,410. Merck has withdrawn U.S. Patent No. 5,681,590 from this lawsuit, and has indicated it may withdraw U.S. Patent Nos. 5,358,941, 5,849,726, 6,008,207 and 6,090,410 from this lawsuit as well. If Merck decides not to withdraw these patents, Teva will withdraw this objection.

General Objection 15

Teva objects to each document request to the extent it seeks information relating to the manufacture of any of the ingredients in the alendronate formulations that are the subject of ANDA No. 75-710.

General Objection 16

Teva objects to definition I as overly broad to the extent it includes entities beyond Teva Pharmaceuticals, USA. For purposes of the document request, responsive documents in the possession, custody or control of Teva Pharmaceuticals, USA will be produced.

General Objection 17

Teva objects to definition BB, except for purposes of the document request

General Objection 18

Teva objects to the use of the term "defendants" in each of the document requests in which it appears because it is confusing. There is only one defendant in this lawsuit, Teva Pharmaceuticals U.S.A., and Teva will interpret the term accordingly.

General Objection 19

Teva objects to the use of the term "formulation [s]" in each of the document requests in which it appears because it is ambiguous. Teva will interpret this term to mean pharmaceutical formulations, i.e. active ingredients mixed with a pharmaceutically acceptable carrier.

General Objection 20

Teva objects to the use of the term "Defendants' certification" in each of the document requests in which it appears because it is confusing and ambiguous. Teva will interpret this term to mean the Teva's certifications relating to the weekly alendronate sodium product that is the subject of ANDA No. 75-710.

General Objection 21

Teva objects to each of the document requests to the extent they seek documents that have been produced in *Merck v. Teva*, Civ. Action No. 00-035 (JJF). By agreement of the parties, documents produced in that lawsuit will be deemed produced in this lawsuit.

RESPONSES TO DOCUMENT REQUESTS

Document Request No. 1

All opinions, legal or otherwise, relating to the validity, invalidity, infringement, non-infringement, enforceability, non-enforceability, liability, or license (either express or implied) to Defendants for any of the patents-in-suit or any other affirmative defense.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 2

All documents and things, including correspondence with counsel, relating to the validity, invalidity, infringement, non-infringement, enforceability, non-enforceability, liability, or license (either express or implied) to Defendants for any of the patents-in-suit or any other affirmative defense.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 3

All documents and things relating to patent clearances, freedom to operate opinions or other mechanisms to avoid infringement or willful infringement by Defendants of any of the patents-in-suit.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 4

All opinions, legal or otherwise, relating to the validity of the patent term extension or the patent term restoration of the '077 patent.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 5

All documents and things, including correspondence with counsel, relating to validity of the patent term extension or the patent term restoration of the '077 patent to Defendants.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 6

All documents and things relating to any policies or practices of Defendants concerning patent clearances, freedom to operate opinions or other mechanisms to avoid infringement or willful infringement by Defendants of the patents of others.

Response

Teva objects to this request to the extent it is overly broad and unduly burdensome in that it calls for documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence.

Document Request No. 7

All Abbreviated New Drug Applications filed by Defendants with the FDA for alendronate formulations or other pharmaceutically active biphosphonate formulations.

Response

Teva objects to this request as overly broad and burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to this and the General Objections, responsive documents relating to the weekly alendronate sodium formulations that are the subject of ANDA No. 75-710 will be produced to the extent they are relevant to the issues in this lawsuit.

Document Request No. 8

All supplements and amendments to Abbreviated New Drug Applications filed by Defendants with the FDA for alendronate formulations or other pharmaceutically active biphosphonate formulations.

Response

Teva objects to this request as overly broad and burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to this and the General Objections, responsive documents relating to the weekly alendronate sodium formulations that are the subject of ANDA No. 75-710 will be produced to the extent they are relevant to the issues in this lawsuit.

Document Request No. 9

All documents and things relating to or constituting correspondence or other communications, including but not limited to draft documents and correspondence, among Defendants and/or between Defendants and/or any other person and any foreign or domestic regulatory agency including, but not limited to, the FDA or a foreign counterpart concerning alendronate or any other pharmaceutically active biphosphonate.

Response

Teva objects to this request as overly broad and burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to this and the General Objections, responsive documents relating to the weekly alendronate sodium amendments to ANDA No. 75-710 will be produced to the extent they are relevant to the issues in this lawsuit.

Document Request No. 10

All documents and things relating to the patent certifications made by Defendants as part of an Abbreviated New Drug Application alendronate formulations or any other pharmaceutically active biphosphonate formulations.

Response

Teva objects to this request as overly broad and burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to this and the General Objections, responsive documents relating to the weekly alendronate sodium formulations that are the subject of ANDA No. 75-710 will be produced to the extent they are relevant to this lawsuit.

Document Request No. 11

All documents and things relating to Defendants' decision to file an Abbreviated New Drug Application alendronate formulations or any other pharmaceutically active biphosphonate formulations, including, but not limited to, the timing of the filing, the cost for the filing, and any cost or benefit analysis.

Response

Teva objects to this request as overly broad and burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to this and the General Objections, responsive documents relating to the weekly alendronate sodium amendments to ANDA No. 75-710 will be produced to the extent they are relevant to the issues in this lawsuit.

Document Request No. 12

All documents and things relating to the timing, schedule, timetable or projection of approval of Defendants' Abbreviated New Drug Application for alendronate formulations or any other pharmaceutically active biphosphonate formulations.

Response

Teva objects to this request as overly broad and burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to this and the General Objections, responsive documents relating to the weekly alendronate sodium amendments to ANDA No. 75-710 will be produced to the extent they are relevant to the issues in this lawsuit.

Document Request No. 13

All documents and things relating to any labeling, promotion, advertising or claims by Defendants for alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any other country.

Response

Teva objects to this request as overly broad and burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to this and the General Objections, responsive documents relating to activities in the U.S. regarding the weekly alendronate sodium product that is the subject of ANDA 75-710 will be produced.

Document Request No. 14

All documents and things relating to Defendants' decision for file a patent certification as part of an Abbreviated New Drug Application for alendronate formulations or any other pharmaceutically active biphosphonate formulation.

Response

See response to request no. 10.

Document Request No. 15

All documents and things relating to FDA notification of "tentative approval"of the 'Abbreviated New Drug Application for Defendants' alendronate formulations.

Response

Teva objects to this request as overly broad and burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to this and the General Objections, responsive documents relating to the weekly alendronate sodium amendments to ANDA No. 75-710 will be produced.

Document Request No. 16

All documents and things relating to the patents-in-suit.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 17

All documents and things relating to the first awareness of the patents-in-suit by Defendants.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 18

All documents and things created before the filing of this suit concerning or constituting any prior art search relating to any of the patents-in-suit.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 19

All prior art that Defendants contend supports an allegation that any claim of the patents-in-suit is invalid.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 20

All documents and things forming the basis of, or relating to, Defendants' certification that any of the patents-in-suit are not, and/or will not be, infringed by Defendants.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 21

All documents and things forming the basis of, or relating to, Defendants' certification that any of the patents-in-suit are unenforceable.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 22

All documents and things forming the basis of, or relating to, any and all defenses pleaded by Defendants that any claim of the patents-in-suit is invalid.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 23

All documents and things forming the basis of, or relating to, Defendants' certification that any of the patents-in-suit are invalid as lacking a written description.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 24

All documents and things forming the basis of, or relating to, Defendants' certification that any of the patents-in-suit are invalid as the specification does not enable the claims.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 25

All documents and things forming the basis of, or relating to, Defendants' certification that any of the patents-in-suit are invalid as indefinite.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 26

All documents and things forming the basis of, or relating to, Defendants' certification

that any of the patents-in-suit are invalid as lacking utility.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 27

All documents and things forming the basis of, or relating to, Defendants' Certification that any of the patents-in-suit are anticipated by the prior art.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 28

All documents and things forming the basis of, or relating to, Defendants' certification that any of the patents-in-suit are invalid as obvious in light of the prior art

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 29

All documents and things relating to the April 21, 1997 patent term restoration of the '077 patent under 35 U.S.C. § 156.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 30

All documents related to Defendants' patent certification and Notice of Patent Certification for Abbreviated New Drug Applications for alendronate formulations.

Response

Teva objects to this request as overly broad and burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to this and the General Objections, responsive documents relating to the weekly alendronate sodium formulations that are the subject of ANDA No. 75-710 will be produced.

Document Request No. 31

All documents and things relating to any legal or administrative proceedings concerning the manufacture, importation, sale, and/or offer for sale of pharmaceutical formulations of alendronate or any other pharmaceutically active biphosphonate in the U.S. by Defendants or any other person.

Response

Teva objects to this request as overly broad and burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to this and the General Objections, responsive documents relating to the weekly alendronate sodium product that is the subject of ANDA No. 75-710 will be produced.

Document Request No. 32

All documents and things concerning any indemnification and/or insurance provided to, received, or granted by Defendants against or for the infringement of any of the patents-in-suit.

Response

Teva objects to this request because it is overly broad and unduly burdensome in that it calls for documents that are not relevant to any issue, and is not reasonably calculated to lead to the discovery of admissible evidence.

Document Request No. 33

All documents and things relating to Defendants' production or attempted production of alendronate formulations or any other pharmaceutically active biphosphonate formulations.

Response

Teva objects to this request as overly broad and burdensome in that it calls for documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence.

Document Request No. 34

All documents relating to research and development of manufacturing processes for alendronate formulations or any other pharmaceutically active biphosphonate formulations.

Response

Teva objects to this request because it is overly broad and unduly burdensome in that it calls for documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence.

Document Request No. 35

All documents and things relating to or comprising communications among Defendants and/or between Defendants and any other person concerning the design, development, testing, structure, function and/or operation of manufacturing facilities for the production of alendronate formulations or any other pharmaceutically active biphosphonate formulations.

Response

Teva objects to this request because it is overly broad and unduly burdensome in that it calls for documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence.

Document Request No. 36

All documents and things relating to U.S. or foreign lawsuits, pending or previously resolved, or investigations regarding Defendants' production of alendronate formulations or any other pharmaceutically active biphosphonate formulations.

Response

Teva objects to this request because it is overly broad and unduly burdensome in that it calls for documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence.

Document Request No. 37

All documents and things relating to any manufacture, importation, sale, and/or offer for sale of pharmaceutical formulations of alendronate or any other pharmaceutically active biphosphonate in the U.S. by Defendants or any other person.

Response

Teva objects to this request as overly broad and burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to this and the General Objections, responsive documents relating to the weekly alendronate sodium product which is the subject of ANDA No. 75-710 will be produced to the extent they are relevant to this lawsuit.

Document Request No. 38

All documents and things relating to any supply agreement for alendronate or any other pharmaceutically active biphosphonate.

Response

Teva objects to this request because it is overly broad and unduly burdensome in that it calls for documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence.

Document Request No. 39

All documents and things constituting or relating to negotiations between Defendants and suppliers or potential suppliers of alendronate or any other pharmaceutically active biphosphonate.

Response

Teva objects to this request because it is overly broad and unduly burdensome in that it calls for documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence.

Document Request No. 40

All documents and things relating to any desire, consideration or need by Defendants to obtain or not obtain a license under any of the patents-in-suit.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 41

All documents and things constituting or relating to licenses and/or agreements for alendronate or any other pharmaceutically active biphosphonate among Defendants and/or between Defendants and any other person.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 42

All documents and things related to licensing agreements among Defendants and/or between Defendants and any other person for the production, distribution or sale of alendronate formulations or any other pharmaceutically active biphosphonate formulations

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 43

All documents and things concerning marketing or whether to market alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any

other country.

Response

Teva objects to this request because it is overly broad and unduly burdensome in that it calls for documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence.

Document Request No. 44

All documents and things relating to market share and market potential for alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any other country.

Response

Teva objects to this request because it is overly broad and unduly burdensome in that it calls for documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to this and the General Objections, responsive documents relating to the weekly alendronate sodium product which is the subject of ANDA No. 75-710 will be produced to the extent they are relevant to this lawsuit.

Document Request No. 45

All documents and things relating to the dollar amounts expended by Defendants or any other person for the promotion of alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any other country.

Response

Teva objects to this request because it is overly broad and unduly burdensome in that it calls for documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence.

Document Request No. 46

All documents and things relating to all forms of promotions for or marketing of alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any other country by Defendants or any other person.

Response

Teva objects to this request because it is overly broad and unduly burdensome in that it calls for documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence.

Document Request No. 47

All documents and things created after January 1, 1993, relating to any market survey, market analysis, sales projections or forecast of customer demand with respect to alendronate formulations or any other pharmaceutically active biphosphonate formulations in the U.S. or any other country.

Response

Teva objects to this request because it is overly broad and unduly burdensome in that it calls for documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to this and the General Objections, responsive documents relating to the weekly alendronate sodium product which is

the subject of ANDA No. 75-710 will be produced to the extent they are relevant to this lawsuit.

Document Request No. 48

All documents and things relating to any communications to or from Defendants' sales forces, agents, dealers, representatives, distributors, the press, or any news wire service relating to this lawsuit, and/or any of the patents-in-suit.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 49

All documents, and things relating to research and development of alendronate and alendronate formulations or any other pharmaceutically active biphosphonate and its formulations.

Response

Teva objects to this request to the extent it is overly broad and unduly burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to the General Objections, responsive documents relating to the weekly alendronate product which is the subject of ANDA No. 75-710 will be produced to the extent they are relevant to the issues in this lawsuit.

Document Request No. 50

Two hundred alendronate tablets for each dosage form produced by Defendants for the

purpose of obtaining FDA approval.

Response

Teva objects to this request to the extent it is overly broad and unduly burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to this and the General Objections, Teva will produce one hundred tablets of each of the weekly alendronate sodium product dosage forms that are the subject of ANDA No. 75-710.

Document Request No. 51

All documents and things relating to any tests comparing Merck's alendronate product with the alendronate product that Defendants produced.

Response

Teva objects to this request because it is overly broad and unduly burdensome in that it calls for documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence.

Document Request No. 52

Any samples of Merck products that contain alendronate or any other pharmaceutically active biphosphonate that have been tested or examined by Defendants or any persons working on their behalf.

Response

Teva objects to this request as overly broad and unduly burdensome and is neither relevant to any issue in this lawsuit nor reasonably calculated to lead to the discovery of

admissible evidence.

Document Request No. 53

All documents and things relating to any testing performed using Merck's alendronate product.

Response

Teva objects to this request because it is overly broad and unduly burdensome in that it calls for documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence.

Document Request No. 54

All documents and things relating to Defendants' knowledge of Merck's activities in the research, patenting, development, manufacture, use or sale of any pharmaceutical formulation of alendronate or any other pharmaceutically active biphosphonate.

Response

Subject to the General Objections, responsive documents will be produced.

Document Request No. 55

All documents and things Defendants contemplate introducing at trial.

Response

Teva objects to this request as premature.

Document Request No. 56

All documents and/or things relating to any experts Defendants contemplate calling at trial, including but not limited to the educational and technical training of each expert and any publications authored by such expert.

Response

Teva objects to this request as premature.

Document Request No. 57

All documents and things, including but not limited to organizational charts, showing identity and job titles of employees since January 1, 1993 to the present for all of Defendants' divisions and/or subsidiaries involved in the research, development, production, design, manufacture or sale of alendronate formulations or any other pharmaceutically active biphosphonate formulations.

Response

Teva objects to this request to the extent it is overly broad and unduly burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to these objections and the General Objections, documents, documents sufficient to describe Teva's organization to the extent it relates to the weekly alendronate sodium product that is the subject of ANDA No. 75-710 will be produced.

Document Request No. 58

All documents and things setting forth Defendants' document retention and/or destruction policies.

Response

Teva objects to this request to the extent it is overly broad and unduly burdensome in that it encompasses documents that are not relevant to any issue in this lawsuit, and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to these objections and the General Objections, responsive documents will be produced.

Document Request No. 59

All documents and things relating to or constituting applications by Defendants to obtain regulatory approval for alendronate or any other pharmaceutically active biphosphonate in a foreign country.

Response

See General Objection 12.

Document Request No. 60

Two grams of each ingredient in the alendronate tablets produced by Defendants for the purpose of obtaining FDA approval.

Response

Teva objects to this request because it is overly broad and unduly burdensome. Subject to this and the General Objections, Teva has already produced a two gram representative sample of the active ingredient in the alendronate product that is the subject of ANDA 75-710 in *Merck*

v. Teva, Civil Action No. 00-035 (JJF) .

YOUNG CONAWAY STARGATT
& TAYLOR, LLP

Josy W. Ingersoll (# 1088)
The Brandywine Building
1000 West Street
Wilmington Delaware 19801
Telephone: (302) 571-6672
Telecopy: (302) 576-3301

James Galbraith
Maria Luisa Palmese
William G. James, II
KENYON & KENYON
One Broadway
New York, New York 10004
Telephone: (212) 425-7200
Telecopy: (212) 425-5288

Attorneys for Defendant
Teva Pharmaceuticals U.S.A., Inc.

463432

CERTIFICATE OF SERVICE

I, Josy W. Ingersoll, Esquire, hereby certify that I caused copies of the foregoing document to be served on April 19, 2002 upon the following counsel of record:

BY HAND DELIVERY

Mary B. Graham, Esquire
Morris, Nichols, Arsht & Tunnell
1201 N. Market Street
Wilmington, DE 19801

BY FEDERAL EXPRESS

Nicholas G. Barzoukas, Esquire
Howrey Simon Arnold & White, LLP
750 Bering Drive
Houston, TX 77057

Josy W. Ingersoll

EXHIBIT C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK & CO., INC., Plaintiff, v. TEVA PHARMACEUTICALS USA, INC Defendant.	C.A. No. 01-048-JJF (Consolidated) ~~CONFIDENTIAL~~ ~~FILED UNDER SEAL~~

MERCK'S MOTION TO COMPEL
PRODUCTION OF DOCUMENTS AND THINGS

MORRIS, NICHOLS, ARSHT & TUNNELL
Mary B. Graham (#2256)
Maryellen Noreika(#3208)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
Attorneys for PLAINTIFF
MERCK & CO., INC.

OF COUNSEL:

John F. Lynch
Nicolas G. Barzoukas
Stephen E. Edwards
Jason C. Abair
HOWREY SIMON ARNOLD
& WHITE, LLP
750 Bering Drive
Houston, TX 77057-2198
(713) 787-1400

Paul D. Matukaitis
MERCK & CO., INC.
One Merck Drive
Whitehouse Station, NJ 08889-0100

Edward W. Murray
Gerard M. Devlin, Jr.
MERCK & CO., INC.
126 E. Lincoln Avenue
Rahway, NJ 07065-0907

November 12, 2002

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK & CO., INC., Plaintiff, v. TEVA PHARMACEUTICALS USA, INC Defendant.	C.A. No. 01-048-JJF (Consolidated) ~~CONFIDENTIAL~~ ~~FILED UNDER SEAL~~

MERCK'S MOTION TO COMPEL
PRODUCTION OF DOCUMENTS AND THINGS

Merck & Co., Inc. ("Merck") hereby moves pursuant to Fed. R. Civ. P. 37 (a) for an order compelling Teva Pharmaceuticals USA, Inc. ("Teva") to conduct a proper search for documents responsive to Merck's document requests and to produce those documents promptly. It has now become evident that Teva has failed to search for and produce documents of numerous employees, including key personnel who worked on the project team for the generic product it seeks to market.

MERCK'S ONCE-WEEKLY FOSAMAX®

This patent infringement case involves Merck patents covering the continuous oral administration of alendronate sodium on a once-weekly dosing schedule which cover Merck's highly successful once-weekly FOSAMAX®. FOSAMAX®, approved by the Food and Drug Administration ("FDA"), is used for the prevention and treatment of the debilitating disease osteoporosis. Teva has submitted to the FDA an Abbreviated New Drug Application ("ANDA") No. 75-710 to obtain approval to market generic versions of once-weekly FOSAMAX® prior to the expiration of Merck's patents.

TEVA'S INSUFFICIENT DOCUMENT SEARCHES

Merck has pursued discovery of Teva's decision to market a generic version of Merck's once-weekly FOSAMAX® and its work to implement that decision. Merck early on served basic document requests, and has now taken several depositions of Teva employees involved in that process.

Teva's document production in response to Merck's document requests was scant, only about 4,900 pages.[1] Merck has repeatedly asked that Teva provide additional documents, such as documents reflecting Teva's own conclusions on the commercial success of once-weekly FOSAMAX® and Teva's analysis of the market for a generic version. The commercial success of once-weekly FOSAMAX® is relevant to rebut Teva's assertions that this inventive idea was obvious.[2] But Merck's inquiries about Teva's facially questionable production have met only with unelaborated assertions of Teva's outside counsel that Teva's searches were "thorough" and that "Teva has produced all responsive documents to Merck."

Teva's outside counsels' representations are simply not correct, as is now abundantly clear from several depositions of Teva witnesses whose files were not adequately

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[1] Merck served its First Requests for Production on March 19, 2002. Teva responded on April 19, 2002 (Exhibit A), and produced about 1,790 pages of documents in early June, 2002 (Exhibit B). The other 3,000 pages of documents were previously produced by Teva in the prior litigation between Merck and Teva. Teva has also produced to Merck approximately 2,310 pages of documents that it obtained from subpoenas of third parties.

[2] Teva has raised the affirmative defense that Merck's patents-in-suit are invalid for obviousness over the prior art under 35 USC § 103. To rebut this defense, Merck will present evidence on the commercial success of once-weekly FOSAMAX®. *See Graham v. John Deere Co.*, 383 U.S. 1 (1966) (commercial success is a secondary consideration negating obviousness). *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-39 (Fed. Cir. 1983); *see also Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986) ("all relevant evidence going to the issue of obviousness/nonobviousness, which includes properly presented evidence on

(Continued. . .)

searched, or searched at all, and from Teva documents revealing that other documents, which have not been produced, must exist. Moreover, counsel's assertions were not based on first-hand knowledge. It turns out that it is in-house counsel who searched for documents.

On September 6, 2002, Teva produced for deposition its first witness, Deborah Jaskot, Teva's Executive Director of Regulatory Affairs, one of only three Teva employees listed in Teva's initial disclosures under Rule 26(a). In response to Merck's questions about documents in her personal files and litigation searches of those files, Ms. Jaskot testified that she is in possession of many relevant documents and folders that were never searched.

In particular, Ms. Jaskot testified that she possesses paper and electronic files (Exhibit C at 142, 146-147), including five years' worth of meeting minutes (*id.* at 151-152), and that Teva maintains a "central ANDA file" (*id.* at 147), marketing forecasts for alendronate sales (*id.* at 123), and internal routing sheets for draft documents, including drafts of documents relating to ANDA 75-710 (*id.* at 47-52). The volume and variety of these documents do not appear in Teva's document production. Ms. Jaskot also testified that, while she recalled producing documents from her personal files for the earlier lawsuit between the parties, she does not recall producing documents in connection with the current lawsuit initiated nearly two years later (*id.* at 148-149).

Following that deposition, Merck wrote to Teva's counsel, detailing the deficiencies in Teva's document production and requesting that Teva's employees' files, including those of Ms. Jaskot, be searched (Exhibits D, E). In response, Teva's counsel, Danae

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(. . . continued.)

> secondary considerations must [be] considered prior to reaching a conclusion on obviousness/nonobviousness").

Schuster, on October 8, 2002 produced, without explanation or response to Merck's specific inquiries, 14 pages of documents purportedly collected from Ms. Jaskot's files (Exhibit F). In a follow-up teleconference, Ms. Schuster informed Merck that the search for the documents described in Merck's letters had been handled entirely by in-house counsel for Teva, and that she had made several requests to Teva's in-house counsel for the documents described in Merck's letters. She further said that the only documents in-house counsel had produced were the 14 pages. When Merck asked about the files of the many recipients listed on these documents, counsel simply reiterated that the 14-page supplemental production from Teva's in-house counsel had addressed Merck's concerns.

After this teleconference, Ms. Schuster by letter dated October 9 produced the most recent version of Teva's package inserts (created in June 2002), without explanation of why Teva had withheld them for four months (Exhibit G). Counsel then asserted simply that, "[w]ith respect to your concern about Teva's document production, all additional responsive documents have now been produced" (*id.*). Despite that representation, however, two weeks later Teva produced without explanation an additional 25 pages at the deposition of its employee Christopher Pelloni on October 23, 2002. Notably, Mr. Pelloni could not remember even the most basic of details about any searches for documents responsive to Merck's requests for production (Exhibit I at 5-11.)

Merck again followed up and asked about the searches of Mr. Pelloni's files and all other employees involved in the alendronate project (Exhibit H). Ms. Schuster called on November 1, 2002 to say only that Teva had purportedly searched for and produced all responsive documents from Mr. Pelloni, and that Teva would provide a response to the rest of Merck's concerns by the end of the day on November 4, 2002 (which we never received).

TEVA DOCUMENTS NOT FOUND IN THE PRODUCTION

Among the 14 pages produced on October 8, 2002 were minutes of two Teva meetings where alendronate was discussed (Exhibit F, T007106 and T007110). These documents went to as many as 28 people who attended the meetings or received the agendas. Teva has not produced, however, any documents from any of these people other than a few purportedly collected from the two Teva employees Merck has deposed, Ms. Jaskot and Mr. Pelloni. It is virtually certain that at least some of the other 26 employees possess other documents responsive to Merck's requests. Furthermore, Ms. Jaskot testified that she took notes at meetings, and that other Teva employees attending these meetings probably took notes (Exhibit C at 128-129). Teva's production of a mere 14 pages cannot possibly reflect all the documents of all relevant Teva employees.

Indeed, Christopher Pelloni testified that the one Teva employee who should be most familiar with Teva's considerations in filing its ANDA is Ms. Anne Payne, who chairs Teva's "product identification team" ("PIT") for alendronate and generates sales forecasts for the prospective generic forms of alendronate and updates to those forecasts (Exhibit I at 39, 40, 120-129). Clearly, Ms. Payne, who is an identified recipient of the minutes, is likely to possess important documents. Yet, Teva has evidently not produced a single document from her files.

The documents Teva has failed to produce relate, *inter alia*, to the commercial success of once-weekly FOSAMAX® in the treatment and prevention of osteoporosis. For example, requests for production nos. 6, 10-14, 16, 17, 43-48 relate to Teva's decision to file ANDA 75-710, Teva's business practices relating to the decision to file ANDA 75-710, and Teva's analysis of the market for the administration of alendronate sodium once per week (Exhibit A.).

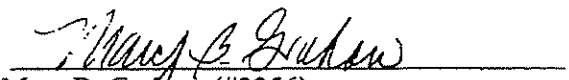
Teva has not produced other important documents, including, *inter alia*, internal and external correspondence relating to ANDA 75-710, internal correspondence between members of Teva's committees and teams, routing sheets containing comments pertaining to ANDA 75-710, all of Ms. Jaskot's paper and electronic files relating to internal committees and teams, documents from Teva's "central ANDA file," and documents from Teva's marketing department including alendronate packaging and marketing forecasts. Considering the number of Teva employees who have received documents relating to alendronate sodium, Teva's failure to search for responsive documents, Teva's miniscule production, and Teva's lack of a document retention policy dictating destruction of documents, Teva's assertion that "all additional responsive documents have been produced" is facially unsupportable.

THE RELIEF NEEDED

Teva's nominal attempts to comply with its discovery obligations and respond to Merck's concerns appear to be primarily limited to searches of (some of) one or two employee files conducted by in-house counsel. Merck submits that Teva should be ordered immediately to produce all responsive documents. Moreover, in view of the testimony of Teva's witnesses and the lack of production of known documents from known Teva employees, the blind reliance of outside counsel upon in-house counsel to conduct searches for documents is clearly insufficient.

Merck requests that Teva be required immediately to conduct a full search for documents, and in view of the history of inadequate production, that Teva's outside counsel conduct the search.

MORRIS, NICHOLS, ARSHT & TUNNELL



Mary B. Graham (#2256)
Maryellen Noreika(#3208)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
ATTORNEYS FOR PLAINTIFF
MERCK & CO., INC.

OF COUNSEL:

John F. Lynch
Nicolas G. Barzoukas
Stephen E. Edwards
Jason C. Abair
HOWREY SIMON ARNOLD
& WHITE, LLP
750 Bering Drive
Houston, TX 77057-2198
(713) 787-1400

Paul D. Matukaitis
MERCK & CO., INC.
One Merck Drive
Whitehouse Station, NJ 08889-0100

Edward W. Murray
Gerard M. Devlin, Jr.
MERCK & CO., INC.
126 E. Lincoln Avenue
Rahway, NJ 07065-0907

November 12, 2002
318885

CERTIFICATION PURSUANT TO LOCAL RULE 7.1.1

Pursuant to Local Rule 7.1.1, I hereby certify that counsel for Merck has made a reasonable effort to reach agreement with opposing counsel on the matters described in the motion to compel, and that the parties were unable to reach any such agreement.

Mary B. Graham

EXHIBIT D

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Alendronate Treatment of Naturally-Occurring Periodontitis in Beagle Dogs*

Michael S. Reddy, Thomas W. Weatherford, III, C. Anne Smith, Brian D. West, Marjorie K. Jeffcoat, Thomas M. Jacks

THE TREATMENT OF PERIODONTAL DISEASE has been largely directed at the microbiological etiology. The prevention of bone loss by modulating the host response to the bacteria may be a useful adjunctive method in the management of periodontitis. Alendronate, an amino bisphosphonate, may inhibit bone loss in osteolytic diseases by altering osteoclast activity. The objective of this double-blind study was to evaluate alendronate inhibition of alveolar bone loss in the naturally occurring beagle dog model of periodontitis. Sixteen 7 to 9 year old beagles with moderate-to-severe periodontitis were studied for 6 months. The dogs were stratified into two groups based on initial periodontal severity. One group received 3.0 mg/kg alendronate weekly orally and the other group received a placebo. Silk ligatures were placed on the study teeth for the first 3 months of the study to exacerbate the periodontal destruction. Clinical data were collected for attachment level, gingival index, plaque index, and mobility at baseline and one-month intervals. Intraoral radiographs were made at baseline and at 3 and 6 months. The mandibles were processed for histolology at month 6. The radiographs were analyzed by digital image analysis of the subtracted images. A statistically significant difference in bone mass ($P < 0.001$) was observed between the alendronate and placebo groups. The bisphosphonate had no effect on the clinical parameters of gingival inflammation or plaque. A trend toward decreased attachment loss and mobility was observed in favor of the alendronate group. A significant difference in bone density ($P < 0.05$) was found by histomorphometric analysis. Bisphosphonate treatment may be beneficial in the management of alveolar bone destruction associated with periodontal destruction. *J Periodontol 1995; 66:211–217.*

Key Words: Bone resorption/prevention and control; periodontitis/drug therapy; bisphosphonates/therapeutic use; double-blind studies.

The periodontal destruction syndrome is initiated by one or more bacterial pathogens. The bacterial species and the immunological response of the host are responsible for the bony destruction observed in the periodontal diseases. The treatment of periodontal disease has largely concentrated on the bacterial etiology, through the use of mechanical instrumentation and surgical alteration of the sites. Pharmaceutical treatment adjuncts have also mainly addressed the bacterial side of the equation through the use of antibiotics and antimicrobials.

In the past 10 years it has been demonstrated that modulation of the host response may play an important role in controlling alveolar bone destruction. Non-antibiotic tetracyclines have been shown to have an anticollagenolytic effect on the periodontium.[1] Non-steroidal anti-inflammatory drugs may have a strong role in the management of the mediators of inflammation associated with alveolar bone destruction.[2] The prevention of the bone loss associated with periodontal disease progression by modulation of the host response may, therefore, be an adjunct approach to the management of periodontitis.

Alendronate, an amino bisphosphonate, is currently under investigation for the treatment of a variety of bone diseases. Earlier studies have indicated that systemic administration of alendronate is rapidly taken up by bone tissues or excreted by the kidneys.[3] Once taken up by bone, the drug acts as an antiosteolytic agent. Alendronate binds to resorption surfaces, and is locally released during the acidification associated with osteoclastic activity. This release leads to a rise in the local concentration of alendronate resulting in an alteration in the ruffled border membrane characteristic of osteoclasts without destroying the cells.[4] Therefore, the mode of action of the bisphosphonate alendronate is believed to be inhibition of bone resorption by altering osteoclast activity.

Bisphosphonates have been utilized to prevent bone loss in ovariectomized animals[5,6] and in estrogen-deficient

*The University of Alabama, School of Dentistry, Department of Periodontics, Birmingham, AL.

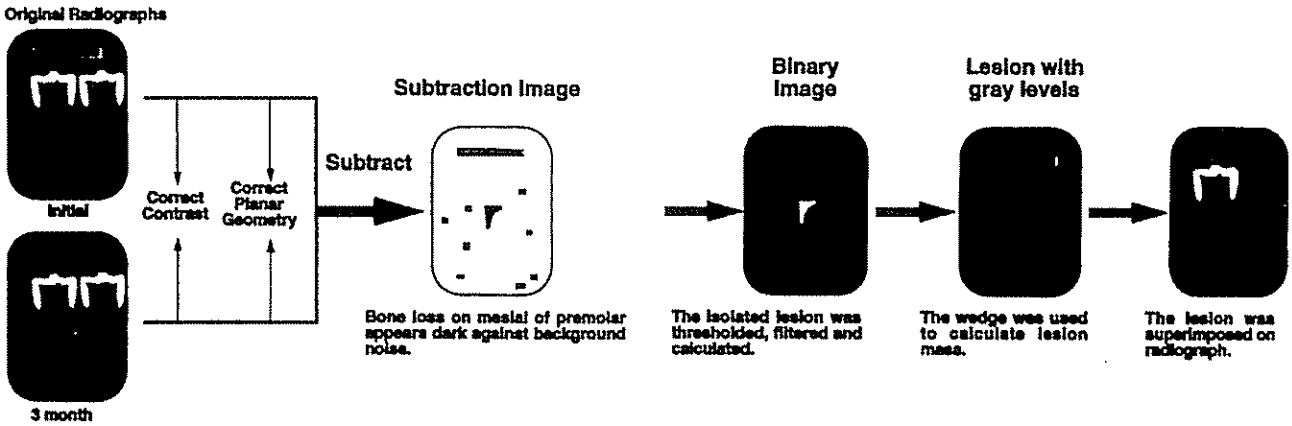

Figure 1. A schematic representation illustrating the image processing methods that were utilized to obtain quantitative measurements of bone loss.

women.[7] Bisphosphonates have been used in the treatment of malignant hypercalcemia,[8] Paget's disease,[9] and osteoporosis.[10] Alendronate may, therefore, have a potential role in the inhibition of alveolar bone loss in periodontal disease.

The beagle dog model, with naturally-occurring periodontal disease, has been utilized extensively as a test environment for potential periodontal therapies. The use of aged adult beagles who are not actively growing allows for a more accurate transition of findings to clinical practice. The classic model of naturally-occurring disease in the dog has been modified in this study by the use of ligatures to induce all sites into an active phase of periodontal destruction. Thereafter the ligatures are removed allowing the natural progression of periodontitis to proceed to a chronic phase. The use of an active and chronic phase in the naturally-occurring dog model may provide a more rigorous challenge for the test of proposed preventive and regenerative periodontal therapy.

The goal of this study was to evaluate the effect of the bisphosphonate drug alendronate on radiographic bone loss and clinical parameters associated with the progression of periodontitis in the naturally-occurring beagle dog model.

MATERIALS AND METHODS

Experimental Design

Sixteen beagles with moderate-to-severe alveolar bone loss were studied for a 6-month period. All animals were 7 to 9 years of age and were female. Clinical measurement of attachment level, gingival index, plaque index, and mobility was performed monthly. Intraoral radiographs were made every 3 months. The radiographs were analyzed by digital image analysis of the subtracted radiographs. At month 6 the animals were sacrificed and examined by histomorphometric analysis.

The dogs were stratified into two groups based on the amount of existing bone loss at the start of the study. In order to activate and accelerate the disease process, silk ligatures were placed on the mandibular premolar teeth for the first 3 months, followed by a 3-month chronic disease progression phase. The ligatures insured that an exacerbation of the disease occurred during the study. The second 3-month phase allowed the activated disease process to progress to a chronic phase.

Dosing and Clinical Examination

This double-blind study was placebo controlled with each dog receiving either alendronate or placebo orally, once a week in the morning before feeding. In order to aid absorption, food was withheld for 2 hours after dosing. The weekly dose was 3.0 mg/kg for both the alendronate and the lactose placebo group.

All examinations were performed without knowledge of the regimen received by each dog. The dosing code was not revealed until all data were analyzed. At one month intervals the following clinical determinations were made at the premolar study sites: gingival index,[11] plaque index;[12] attachment level measurement from the cemento-enamel junction to the base of the periodontal pocket using a Michigan O Probe; and mobility.[13] All clinical examination parameters were made by the same examiner throughout the study.

Radiographic Exam and Analysis

Standardized intraoral radiographs were made by fabricating custom occlusal registration appliances for each radiographic projection. An aluminum reference wedge was incorporated in each custom film holder to provide a density reference. In order to assure that the radiographs were assessed without knowledge of the identity of the dog or treatment group, a random number table was used to code each radiographic series.

A personal computer-based image processing work station was used to obtain quantitative measurements (Fig. 1) of bone loss. For each measurement, the radiograph was placed under a video camera and digitized with 512 × 512 pixels of spatial resolution and 8 bits (256 gray levels) of

contrast resolution. The first radiograph was digitized and stored on an optical disk. The subsequent radiographic image was aligned to the initial image by manipulating it under a video camera. The images were corrected for variations in contrast and film tilt using computer algorithms.[14,15] The second radiographic image was then subtracted from the first, with the resultant subtraction image showing areas of bone loss (dark areas) and bone gain (light areas) against a neutral gray background. Measurements of bone loss or gain were made along each root surface interactively using a mouse as the pointing device.

The estimate of bone mass change was achieved by converting the subtraction image to a binary image of black and white using a variable operator-controlled threshold. The operator adjusted the threshold until the change appeared white against a background which was black. A morphologic filter was applied to the image to limit the remaining noise in the image.[16] An erode operation was performed on the binary image to remove isolated pixel noise. A dilate operation was then performed on the binary image to remove isolated pixel noise. A dilate operation was then performed to restore the areas of bony change to their approximate original size. Pseudocolor image enhancement was used to represent areas of bone gain as green and areas of bone loss as red.[17] Regions of no change were displayed as the original shades of gray. The color-enhanced image was electronically added to the original radiograph so that the area of change could be visualized on the original radiographic image (Fig. 1). A comparison of the mean change in gray level at the color enhancement region to the gray levels from the subtraction image of the reference wedge allowed calculation of the thickness of the lesion. The thickness and area measurements were used to calculate an index of bone mass change. Previous studies have indicated that the error in repeatability of determination of areas was 4% and that calculated changes in bone mass correlated ($r^2 > 0.9$) with actual changes in bone mass.[16]

Histomorphometric Analysis

At month 6 the animals were sacrificed and the mandibles, including the test teeth and soft tissue, were removed and fixed in 10% buffered formalin. The specimens were demineralized in 15% formic acid for 2 weeks, dehydrated in increasing ethanol solutions, and embedded in methyl methacrylate. Frontal (bucco-lingual) serial sections (6 mm thick) were cut through mid-furcation areas of second, third, and fourth premolars perpendicular to the long axis of the mandible so as to include the most coronal portion of the buccal and lingual bone and inter-radicular spaces.[18] Sections were deplastified in warm xylene overnight and stained with Masson's trichrome stain.

Quantitative analysis of bone density was determined by the aerial fraction of bone as it relates to its volume. The volume was ascertained using uniform weight and density 5 × 7 black and white photography paper.[19] The central sections of each dog's mandible were photographed at × 45 magnification. These photographs were made of uniform areas at the apices of the teeth sectioned. Weights being equal, areas of volume were determined, and density established by weighing the amount of mineralized versus non-mineralized component of bone. With each photograph, the bone was out of the picture using a surgical scalpel blade. The bone was weighed using an analytical balance measuring to the nearest milligram. The print of the bone was further sectioned into mineralized and non-mineralized components and weighed individually. These differences in mass of mineralized and non-mineralized bone were then converted into relative percentages for each photographed section. The resulting percentages were then interpreted into the relative densities of the bone.

Statistical Analysis

The data presented in this report were derived from analysis of variance measures (ANOVA) for each outcome parameter. The dogs and not the site or teeth were used as the unit of analysis between groups. The ANOVA model therefore corrected the error term to account for the nesting of tooth sites within dogs. Teeth that were lost during the study were included in the analysis to that point in time and were statistically treated as equivalent to the most severely involved sites.

RESULTS

Bone Mass and Bone Height

Bone mass was the primary outcome variable for the study. The bone mass or mg equivalents of bone were measured from a reference wedge incorporated into the radiographic films used for digital subtraction radiography. Figure 2 indicates the change in mg of bone for the two groups at 3 and 6 months. From baseline to 3 months, both groups lost bone with no significant difference between the groups. At this point both groups had silk ligatures tied on the study

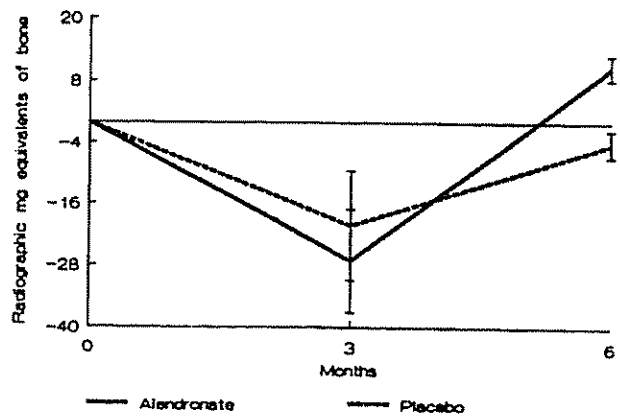

Figure 2. The change in bone mass at 3 and 6 months for the alendronate and placebo groups. A statistically significant difference between the groups was observed at 6 months.

teeth. Following removal of the ligatures both groups demonstrated a gain in bone mass. The alendronate group, however, demonstrated an increase in bone mass above baseline in spite of the activated periodontitis. The placebo group also demonstrated an increase in bone mass which did not recover to baseline. At 6 months a highly significant ($P < 0.001$, ANOVA) difference in bone mass was found between the alendronate and placebo groups.

In addition, the administration of alendronate had an effect on bone height when compared to the placebo group (Fig. 3). Both groups lost bone height when the ligatures were in place during the first 3 months. The placebo group continued to lose bone height at a decreased rate during the second 3 months, whereas a significant rebound in bone height ($P < 0.01$, ANOVA) almost to baseline was noted in the alendronate group at 6 months.

Overall, the alendronate group lost 0.2 ± 0.1 mm and the placebo group 1.4 ± 0.1 mm of bone height during the 6-month study.

Plaque Index

Figure 4 illustrates the clinical measurement of plaque on the teeth on a 4-point scale from 0 to 3, with 3 being severe plaque accumulation on the teeth. The data illustrated no change in plaque over time and no change in either group from baseline. A separation in the groups was observed at the 4-month time point that was not sustained at 5 and 6 months.

Gingival Index

Figure 5 illustrates the gingival inflammation observed over time. The GI scale was again based on clinical observations on a scale of 0 to 3, with 3 being the most severe gingival inflammation. There was no change in the gingival inflammation observed over the course of the study. Similarly, there was no significant difference in inflammation between groups.

Attachment Level

Clinical attachment level was measured with a periodontal probe from the cemento-enamel junction to the base of the periodontal pocket. A decreasing number represented a gain of attachment level. Figure 6 indicates the mean attachment loss for each group over time. The groups tended to show a difference at 6 months favoring the alendronate group. However, when we examined the change in attachment level relative to baseline (Fig. 7) the difference was not significant; although a trend for the alendronate group to have less attachment loss than the placebo group was still readily apparent.

Mobility

Mobility was measured as movement to a lateral force. A mobility of 1 indicated 1 mm of movement. The scale for mobility was from 0 to 3. Figure 8 indicates that when the 6-month data were compared to the time 0 data, the alendronate group showed a decrease in mobility whereas the

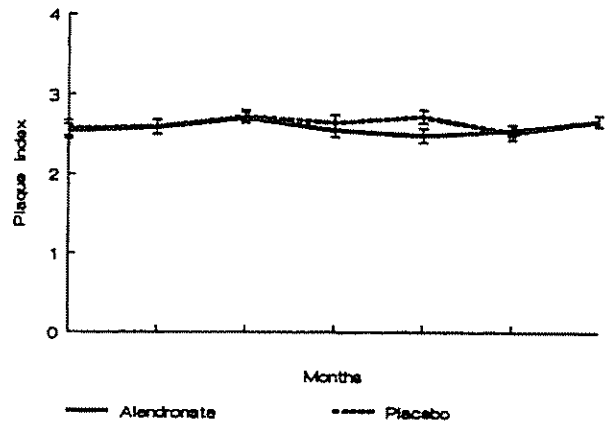

Figure 4. The plaque index for the alendronate and placebo groups measured at one-month intervals. No effect on plaque levels was evident during the study.

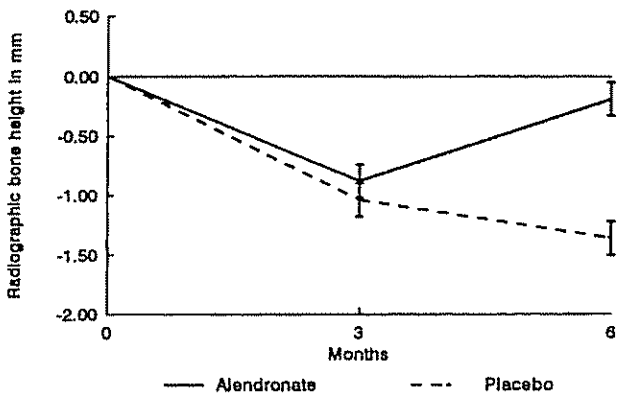

Figure 3. The change in bone height at 3 and 6 months for the alendronate and placebo groups. The placebo group demonstrated significantly more bone loss at 6 months.

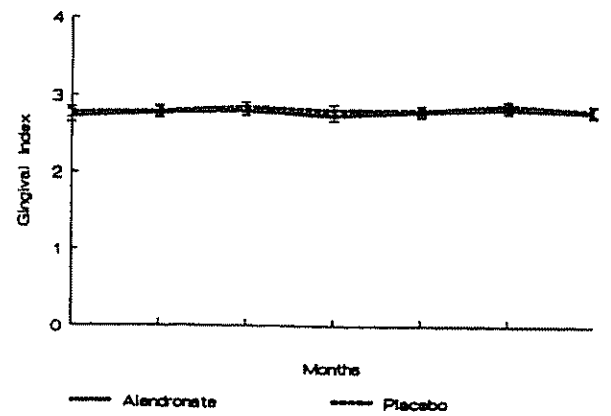

Figure 5. The gingival index for the alendronate and placebo groups measured at 1-month intervals. Consistently high gingival inflammation was observed in both groups.

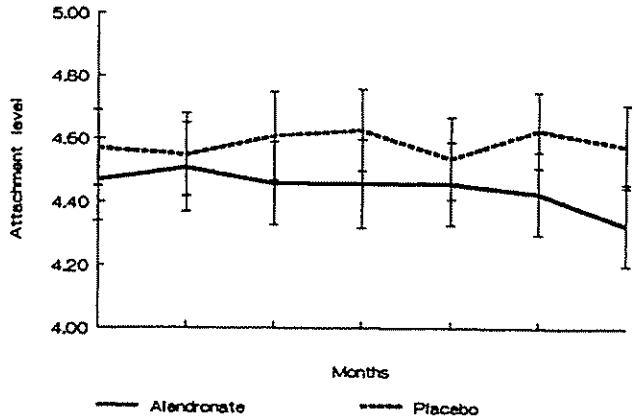

Figure 6. The change in attachment level measured at 1-month intervals. A decrease in the attachment level measurement indicates a gain in clinical attachment. A trend favoring the alendronate group was observed.

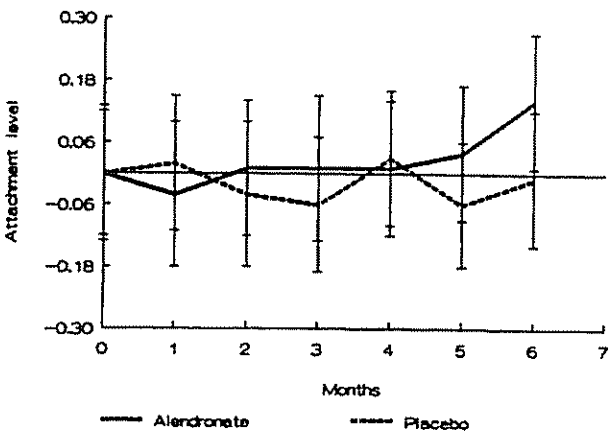

Figure 7. A re-analysis of the change in attachment level correcting for the amount of attachment at baseline. A positive change in attachment level represents a gain in clinical attachment. No significant change in attachment level was observed after correction for the baseline amount of attachment loss.

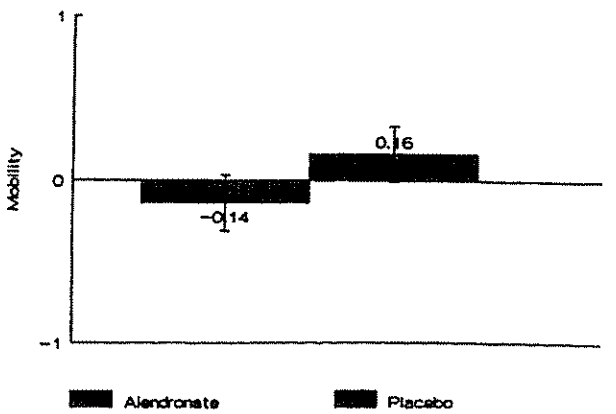

Figure 8. The change in mobility at 2 months. The alendronate group demonstrated decreased mobility whereas a trend for increased mobility was observed in the placebo group.

placebo group showed a trend toward increased mobility. Figure 9 demonstrates the change in mobility over time relative to the initial mobility of the teeth. In the last 3 months, the alendronate group had a tendency toward a decrease in mobility when compared to the control group.

Histomorphometric Analysis

The histological sections were examined to determine the amount of mineralized cortical and trabecular bone versus non-mineralized medullary space present in the central bucco-lingual sections of the alveolar bone at each test tooth site. The mean percentage of mineralized bone for the alendronate and placebo groups is illustrated in Figure 10. A statistically significant difference in bone density was observed between the groups at the end of the study. This difference may represent prevention of the loss of bone density by administration of alendronate or a gain in density induced by the drug. Overall, the mean percentage of mineralized bone for the alendronate group was $96.8 \pm 1.8\%$ and $85.2 \pm 4.7\%$ for the placebo group ($P < 0.05$, AN-

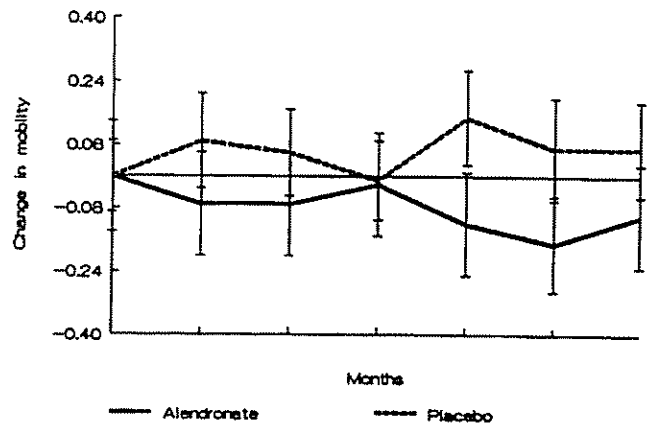

Figure 9. The change in mobility relative to baseline for the alendronate and placebo groups at one-month intervals.

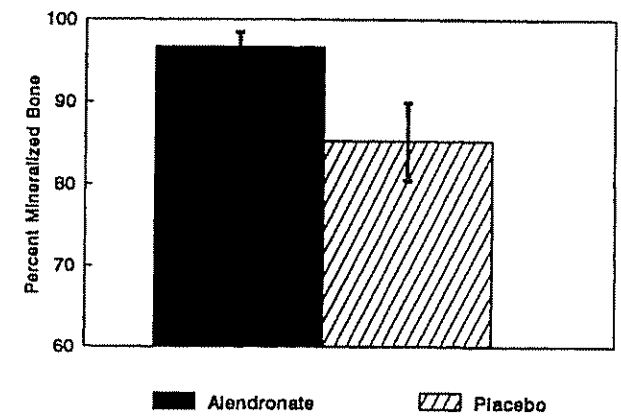

Figure 10. The mean percentage of mineralized tissue found on histomorphometric analysis of the alendronate and placebo groups at 6 months.

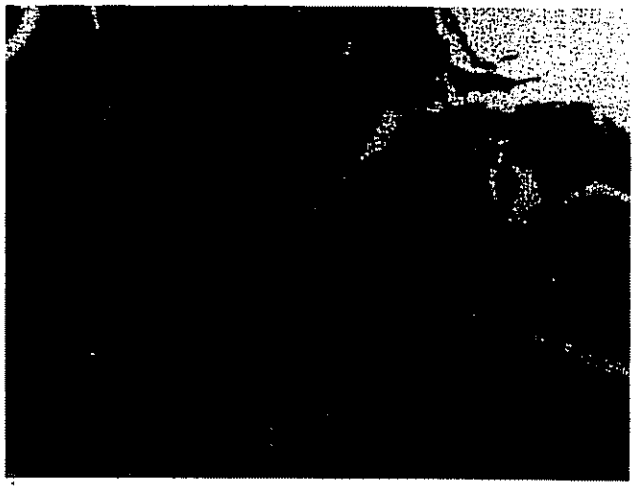

Figure 11. A bucco-lingual section of an alendronate treated dog demonstrating that most of the section is mineralized bone.

Figure 12. A bucco-lingual section of a placebo treated dog showing a higher proportion of non-mineralized connective tissue in the alveolar bone of the bisphosphonate treated example.

OVA). Examples of typical sections from the alendronate (Fig. 11) and placebo (Fig. 12) groups show a striking difference in the amount of trabecular bone present. The bone in the alendronate group appears within normal limits without the mottled appearance often described in histologic sections of bisphosphonate treated bone.

DISCUSSION

The beagle dog model for naturally-occurring periodontal disease was utilized in this study. In the absence of oral hygiene measures, as beagles age they will develop gingival inflammation, periodontal pockets, alveolar bone loss and tooth mobility which are very similar to human periodontitis. The beagles in this study were 7 to 9 years of age and had developed moderate-to-severe periodontitis as determined by clinical and radiographic examinations. In previous studies where a similar experimental design was used to test a potential pharmacological agent in beagles and subsequently in human subjects, comparable results were observed in both the beagle model and in the patients.[2,20]

To further exacerbate the periodontal condition of the dogs, silk ligatures were utilized on the study teeth for the first 3 months of the study. This approach is unique in that both the chronic naturally-occurring model and the acute ligature model of periodontal disease progression in the beagle dog were considered. The effectiveness of any adjunctive agent may depend on the disease activity of the host being examined. This was exemplified by the bone mass, bone height, and attachment level data. With the ligatures in place, a decrease in bone mass was observed for both the alendronate and placebo groups during the first 3 months. After removing the ligatures both groups tended to recover during the chronic phase. The alendronate group made a striking gain in bone mass beyond the mass at the start of the study. The placebo group bounded back slightly after ligature removal but never back to the level at baseline. Overall, the alendronate group gained bone mass, while the placebo group lost bone mass during the study. The alendronate group and placebo group both lost bone height during the ligature phase. After ligature removal, the alendronate group gained bone height, while the placebo group continued to lose bone support. The standard error of the radiographic bone measurements was greater at 3 months than at 6 months. The variance may be due to the different response of some of the animals to the presence of the ligatures on the teeth.

The change in attachment level data showed a similar trend in which the alendronate group tended to gain attachment level in the last 2 months whereas no change in attachment level was observed in the placebo group. The placebo group tended to show loss of attachment during the acute ligature phase, but no attachment loss was evident in the alendronate group. Overall, the tendency for attachment level gain in the alendronate group was not found to be statistically significant. The bisphosphonate therapy was effective in preventing the loss of attachment that was observed in the placebo group during the first 3 months of the study.

The histological analysis demonstrated a significant difference in bone density favoring the alendronate group. Since the histomorphometric analysis only examines the 6-month time point it can be inferred that the bone density difference represents a prevention of loss of bone density due to periodontitis in the treatment group. However, in 7 to 9 year-old dogs the difference between groups observed may be a gain in bone density beyond baseline in the alendronate group.

The gingival index and plaque index demonstrated no difference between the bisphosphonate-treated group and the control group. This result is consistent with previous findings. Bisphosphonate administered intravenously in monkeys retarded the progression of experimental perio-

dontitis as measured by bone density but did not significantly affect the clinical indices of plaque and gingival inflammation.[21] The present study is unique in that it demonstrates an effect on bone at the clinical radiographic and histologic levels after administration of a bisphosphonate orally. Further, the weekly oral dose of alendronate inhibited periodontal progression. If the mechanism of action of the bisphosphonate treatment is directly on bone by alteration and inhibition of osteoclasts, then we would not expect alendronate to have any effect on plaque or inflammation. This may be clinically very important in that the action of the bisphosphonate is independent of the bacterial plaque accumulation present. Therefore, bisphosphonate therapy may be combined with conventional periodontal treatment directed against the microbiological aspects of the disease and also utilized in conjunction with regenerative therapies. The use of bisphosphonates in combination with mechanical surgical approaches, bone grafting, and dental implants may be potential applications of bisphosphonate therapy. Moreover, alendronate accumulates in the bone and may provide protection after the administration of the drug has stopped.

The use of alendronate in beagles with active periodontitis has clearly demonstrated that administration of a bisphosphonate reduced bone loss associated with periodontitis progression. The administration of alendronate may provide a strong adjunctive effect in the management of adult periodontal patients. The use of bisphosphonates may ultimately be added to the armamentarium of the periodontist.

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Send reprint requests to: Dr. Michael Reddy, UAB School of Dentistry, UAB Station 34, 1919 7th Avenue South, Birmingham, AL 35294-0007.
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EXHIBIT E

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

MERCK & CO., INC., Plaintiff, v. TEVA PHARMACEUTICALS USA, INC. Defendant.	)	Civil Action No. 01-048 (JJF) ~~CONFIDENTIAL SUBJECT TO PROTECTIVE ORDER~~

EXPERT REPORT OF GRAHAM RUSSELL

I. QUALIFICATIONS

I am currently the Norman Collison Professor of Musculoskeletal Sciences in the Nuffield Department of Orthopaedic Surgery at the University of Oxford, UK. I am a British citizen. I graduated with First Class Honors in Biochemistry from the University of Cambridge in 1962, and subsequently gained my Ph.D. from the MRC Mineral Metabolism Unit at the University of Leeds. In 1965, I joined Dr. Herbert Fleisch's Medical Research Institute in Davos, Switzerland, and our collaborative work led to the discovery of the biological effects of bisphosphonates. I then moved to Oxford University, where I continued research based at the Nuffield Department of Orthopaedic Surgery. My work with Roger Smith led to the first successful clinical application of bisphosphonates to Paget's disease of bone. Between 1967 and 1971 I completed my medical degree with distinction, having previously completed my pre-clinical studies at Cambridge. I held the Medical Research Fellowship at St. Peter's College from 1972-76. I was awarded my D.M. at Oxford in 1976, and also gained Membership and subsequently Fellowship in the Royal Colleges of Physicians and of Pathology.

During the 1970s, I held appointments in the University of Berne with Herbert Fleisch, and at Harvard University with John Potts and Stephen Krane as the Chiefs of the Endocrine and

Arthritis Units respectively at the Massachusetts General Hospital, before moving in 1976 to the Department of Chemical Pathology in the University of Sheffield Medical School, under the leadership of Jack Martin. I became Professor and Head of the Department of Human Metabolism and Clinical Biochemistry in 1977. Over the following years, I helped to establish Sheffield as a major international center for the study of basic and clinical aspects of bone diseases, and my group has nurtured many clinicians and PhDs who now hold senior positions in the field.

I have worked on topics related to calcium metabolism and bone diseases throughout my career and I am author of more than 480 publications. I have played a central role in studying the biological effects of bisphosphonates, and in their clinical evaluation for the treatment of bone disorders, now including cancer metastases in bone and osteoporosis. My other research interests include bone cell biology, the role of cytokines and hormones, and the pathogenic mechanisms involved in tissue destruction such as occurs in rheumatoid arthritis and osteoarthritis. Current research activities also include studies in myeloma, bone metastases, and other skeletal disorders. My clinical research interests include metabolic bone diseases and osteoporosis, the evaluation of new therapeutic agents and their mode of action, the pharmacology of bone and cartilage, and the use of biochemical methods for monitoring bone and joint metabolism.

I currently hold several national and international appointments in scientific and charitable activities related to bone disease and arthritis. For the Nuffield Foundation (UK), I am Chairman of the Oliver Bird Committee, which is a segment of the Foundation that funds rheumatology research. I am Chairman of the Scientific Advisory Committee of the National Association for Paget's Disease (UK), and a recent member of the Research Advisory Committee for Research into Aging. I am also a member of the Medical Advisory Panel of the

Paget's Foundation in the United States. In April 1997, I was co-Chairman of the 25th European Symposium for Calcified Tissues held in Harrogate, UK. From 1998-2001, I was the President of the International Bone and Mineral Society, the longest established international academic society in this field. From 2000 to 2002 I am serving as Chairman of the Council of Management of the National Osteoporosis Society (NOS, UK), the largest national charity devoted to osteoporosis.

I was Heberden Orator of the British Society of Rheumatology in 1993, received the John B. Johnson award from the Paget's Foundation (USA) in 1997, and the Kohn award of the NOS in 2000. I received the W.F. Neuman award of the American Society of Bone and Mineral Metabolism in 2000. This is the most senior award of the ASBMR and I was the first British scientist to receive it. I was elected a Fellow of the Academy of Medical Sciences (UK) in 2000.

In 2001, I was appointed to the newly established Norman Collison Chair of Musculoskeletal Sciences at Oxford University and I am the first Director of the Oxford University Institute of Musculoskeletal Sciences (also known as the Botnar Research Centre) which opened in 2002. I am a Professorial Fellow at St. Peter's College, University of Oxford.

I have been retained by Kenyon & Kenyon to give my opinions regarding certain aspects of this litigation. My opinions are set forth in detail below. A copy of my curriculum vitae is attached as Exhibit A. In addition to the opinions set forth here, I may respond to the opinions and testimony of Merck's witnesses regarding these issues.

II. SUMMARY OF OPINIONS

1. Claims 1-4, 6, 7, 16-19, 21, 22, 30-32, 35, and 36 of the '329 patent are anticipated by the April 1996 *Lunar News*.

2. Claims 1-4, 6-9, 16-19, 21-23, 30-33, and 35-37 of the '329 patent are anticipated by the July 1996 *Lunar News*.

3. Claims 1-3 of the '329 patent are anticipated by Reddy, J. Periodont. 66(3), 211-17 (1995).

4. Claims 1-4, 6 and 7 of the '329 patent are anticipated by PCT publication WO 95/30421 (Goodship).

5. As of July 1996, the administration of alendronate sodium once per week at a dose sufficient to inhibit bone resorption would have been obvious to a person of ordinary skill in the art.

6. In particular, as of July 1996, the administration of alendronate sodium once per week at a dose of 70 mg to treat osteoporosis would have been obvious to a person of ordinary skill in the art. Likewise, as of July, 1996, the administration of alendronate sodium once per week at a dose of 35 mg to prevent osteoporosis would have been obvious to a person of ordinary skill in the art.

7. As of July 1996, the use of a "kit" consisting of a blister pack and more than one alendronate sodium tablet for administration on a weekly basis would have been obvious to a person of ordinary skill in the art.

8. The above statements are likewise true at any time between July 1996 and July 22, 1997, the filing date of Merck's first provisional application from which the '329 and '294 patents claim priority.

III. BASIS FOR OPINIONS

A. Background

Bone is made up of mineral, a fibrillar organic matrix (about 90 percent collagen), cells and water. The mineral portion accounts for about two-thirds of the total dry weight of the bone. The main constituent of the mineral is calcium phosphate, although it is more correctly referred to as imperfectly crystalline hydroxyapatite. The mineral also contains many other constituents

	would have been recognized by a person of skill in the art to be inherent in the Lunar News disclosure.
. . . orally administering to said human . . .	The reference teaches oral administration of alendronate.
. . . a pharmaceutically accepable amount of alendronate monosodium trihydrate as a unit dosage . . .	The reference teaches the use of higher unit dosages of alendronate on a less frequent basis. Moreover, the reference teaches that single doses of alendronate were shown to have sustained biological responses in patients. Thus, a person of skill in the art would have understood that the reference was teaching the use of "pharmaceutically effective" amounts of the compound, and would have expected such a regimen to be effective. The only approved form of alendronate on the market at that time was alendronate monosodium salt trihydrate, *i.e.*, the active ingredient of Fosamax.
. . . according to a continuous schedule having a once-weekly dosing interval.	The April 1996 *Lunar News* teaches the use of higher doses of alendronate on a weekly basis.

3. Reddy anticipates claims 1 through 3 of the '329 patent

Reddy, J. Periodontology, 66, 211-17 (1995), discloses the once-weekly oral administration of alendronate to beagle dogs with experimentally induced periodontal disease. The study utilized 7 to 9 year old female beagles that had silk ligatures applied to the mandibular premolar teeth for the first three months of the study. After three months the ligatures were removed in order to mimic a chronic progression phase. The author states that results obtained with this particular beagle model have been comparable to those seen in human patients. The double-blind study involved each of the dogs receiving either alendronate or placebo orally once a week in the morning two hours prior to feeding.

Reddy discloses that "The use of alendronate in beagles with active periodontitis has clearly demonstrated that administration of a bisphosphonate reduced bone loss associated with periodontitis progression. The administration of alendronate may provide a strong adjunctive effect in the management of adult periodontal patients."

The Reddy article anticipates at least claims 1 through 3 of the '329 patent. The correspondence between the Reddy disclosure and claim 3 of the '329 patent is shown below.

'329 Patent Claims	Reddy et al.
3. A method for inhibiting bone resorption in a mammal in need thereof . . .	Reddy discloses a method for inhibiting the increased bone resorption associated with periodontitis progression in a beagle dog model. (*See e.g.*, pp. 216-217)
. . . comprising orally administering to said mammal . . .	Reddy discloses oral administration of alendronate to the beagles. (*See e.g.*, p. 212)
. . . a pharmaceutically acceptable amount of . . . alendronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof . . . as a unit dosage . . .	Reddy discloses the administration of "alendronate," which would comprise either alendronic acid, alendronate sodium (or another salt), or mixtures thereof, in amounts that are effective at inhibiting bone resorption.
. . . according to a continuous dosing schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.	Reddy discloses once-weekly administration of alendronate to the beagles for six months. (*See e.g.*, p. 212)

4. The Goodship publication anticipates at least claims 1 through 4, 6 and 7 of the '329 patent

Goodship concerns the administration of bisphosphonates to prevent prosthesis loosening and prosthesis migration. It discloses that arthroplasty (surgical reconstruction of a joint) is common for the treatment of people with osteoporotic fracture, among other things. Goodship discloses the use of bisphosphonates, including alendronate, i.e., "4-amino-1-hydroxybutane-1,1-disphosphonic acid,. . ., a pharmaceutically acceptable salt thereof, and any hydrate thereof" (p. 5), for the prevention and treatment of periprosthetic osteolysis following arthroplasty. Goodship states that the compound may be administered orally, and that "the dose mentioned above – either administered as a single dose (which is preferred) or in several partial doses – may be repeated, either once daily, once weekly, once every month, once every three months, once every six months or once a year." (p. 7). The application of the Goodship disclosure to the claims is set forth in the table below.

CERTIFICATE OF SERVICE

I, Karen L. Pascale, Esquire, hereby certify that on June 5, 2006, I caused to be served a true and correct copy of the foregoing ***Defendant Teva Pharmaceuticals USA, Inc.'s Opening Brief in Support of Its Motion Under Fed. R. Civ. P. 11(b) for Sanctions Against Counsel for Plaintiff Merck & Co., Inc.*** on the following counsel of record:

By Hand Delivery

Mary B. Graham
MORRIS, NICHOLS, ARSHT & TUNNELL LLP
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200

By FedEx

John F. Lynch
HOWREY, LLP
750 Bering Drive
Houston, TX 77057
713-787-1400

Nicolas G. Barzoukas
Suzy S. Harbison
Jason C. Abair
WEIL, GOTSHAL & MANGES
700 Louisiana, Suite 1600
Houston, TX 77002
713-546-5000

Paul D. Matukaitis
MERCK & CO., INC.
One Merck Drive
Whitehouse Station, NJ 08889-0100
908-423-1000

Edward W. Murray
Gerard M. Devlin
MERCK & CO., INC.
126 E. Lincoln Avenue RY28-320
Rahway, NJ 07065-0907
732-594-4000

Karen L. Pascale (No. 2903)